Report

National Heart, Lung, and Blood Institute

Working Group on Heart Disease Epidemiology

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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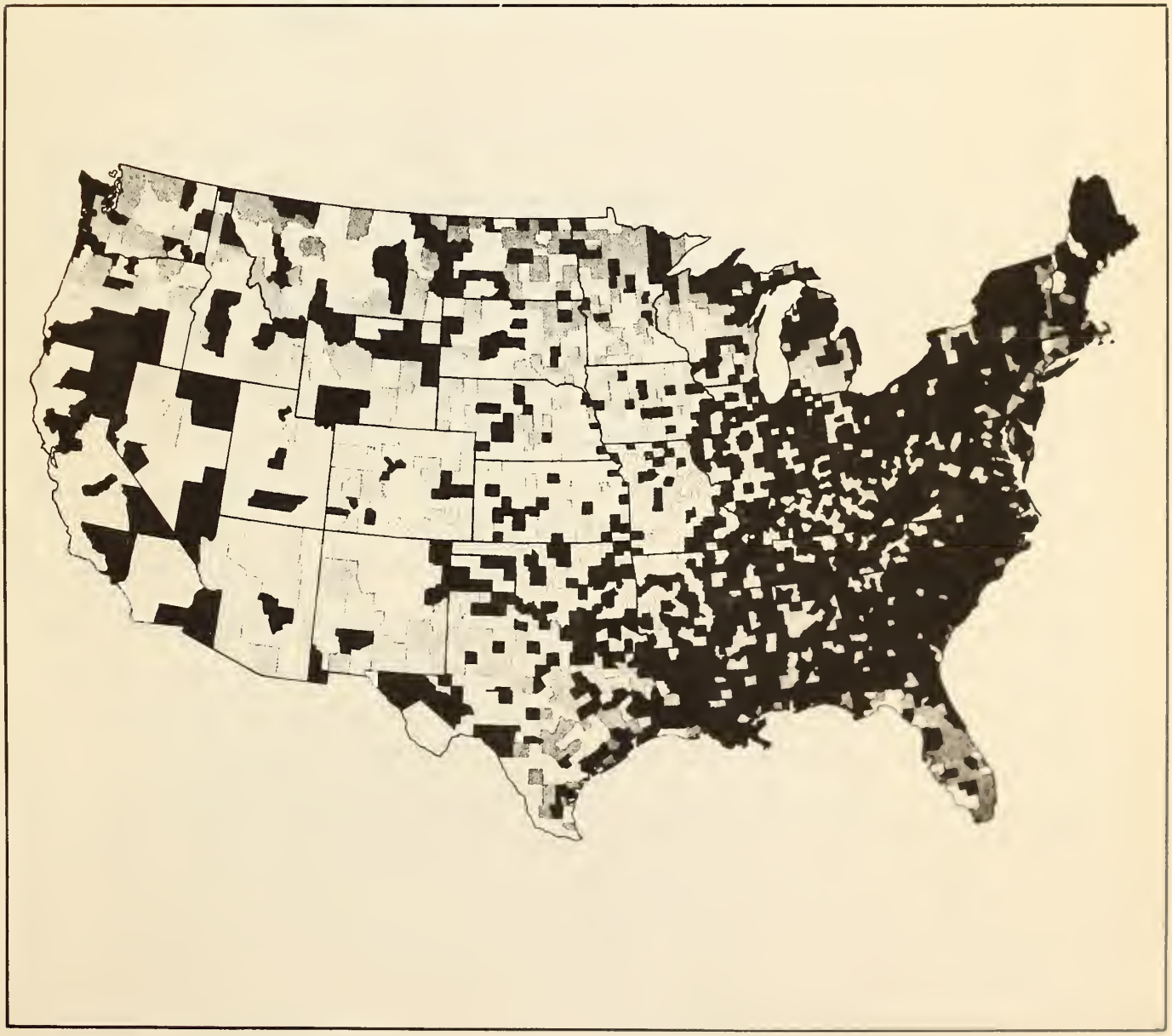

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Background and Summary of Recommendations

This report has been prepared at the request of the Director of the National Heart, Lung, and Blood Institute (NHLBI), in response to the House Subcommittee on the Departments of Labor and Health, Education, and Welfare of the Committee on Appropriations of the House of Representatives. The working group wishes explicitly to indicate its appreciation to the House Subcommittee for its concern and interest.

I. Background

One of the most important recent developments in regard to the major cardiovascular diseases (CVD) and their largest specific component--coronary heart disease (CHD)--is the accelerated decline in mortality rates recorded since the late 1960's. From 1968 to 1976, the mortality rate from premature CHD, for the age group 35-74, declined 24 percent. Over the same period, the death rate from cerebrovascular disease (stroke) fell 33 percent. As a consequence of these dramatic developments, the death rate from all major cardiovascular diseases dropped 25 percent, and the death rate from all causes declined by 17 percent. This trend has been recorded for all four major sex-color groups in the United States: white men, white women, black men, and black women (table 1 and figure 1). The decline in death rate is all the more significant, since for the largest and most devastating form of premature cardiovascular disease, heart attack, the rates had been increasing--at least for men--during the preceding decades. Thus, a steep rise in heart attack death rates was recorded from 1940 into the 1950's, with a continuing less marked rise from the 1950's into the 1960's (figure 1 and table 2). The steady decline over the last 8 to 9 years has brought the mortality rates for middle-aged men back down to approximately the 1940 levels. This fall is all the more impressive, and calls all the more for detailed attention, in view of the fact that mortality rates continue to rise in several other industrialized countries that are also experiencing the devastating effects of the coronary epidemic.

The trends of the past years demonstrate clearly that the CHD epidemic--like all previous epidemics--is amenable to control. This conclusion is buttressed by the dramatic experiences of recent decades in regard to two other cardiovascular diseases that were scourges not too long ago--rheumatic heart disease and cardiovascular syphilis.

The main thrust of this report is to indicate key areas of epidemiologic research needed to deepen understanding of today's major cardiovascular diseases, their trends in the population, their precursors and causes, and consequently, the optimal approaches to furthering the control effort.

The importance of this task is highlighted not only by the possibilities indicated by the trend of recent years, but also by the continuing impact of the major cardiovascular diseases. Despite the recent progress, cardiovascular diseases continue to take a high toll in our population. In 1976, they were responsible for a majority of all deaths (974,429, or 51.0%). Of these CVD deaths, fully two-thirds (646,073) were due to coronary heart disease; about one-quarter of these were fatal heart attacks

that occurred in the prime of life, prior to age 65. An additional 188,623 CVD deaths (19.4% of the total) were due to strokes. Together, coronary heart disease and stroke accounted for 834,696 deaths.

In addition, CHD remains year after year the single most important cause of full disability allowances before age 65 for all major sex-color groups (based on statistics from the Social Security Administration). It is also the single most important cause of days of hospitalization. The high rates for men in the prime of life make CHD a major contributor to family disruption, widowhood, and human misery. The costs in dollars (direct and indirect) make up a sizable part of the huge and ever-rising expenses for medical care in the United States.

Thus, there are reasons--scientific, social, and economic--to go forward with the epidemiologic research effort aimed at maximizing the opportunity for the prevention and control of these diseases.

Over the last three decades, the cardiovascular research community in the United States has developed a vast investigative effort to acquire the knowledge necessary to overcome our all-too-limited understanding of the nature and causes of the major cardiovascular diseases. This effort has utilized every approach of modern research--animal-experimental, pathologic, clinical, and epidemiologic. The broad approach to cardiovascular research has been possible thanks to the sustained commitment and the generous support of the Congress to NHLBI, and the direct contributions of the public to research through voluntary and philanthropic channels.

The epidemiologic effort, the theme of this report, has also made important contributions. International studies have compared rates of CHD in different populations across the globe and have explored the factors that are possibly accounting for the rates. These studies have unequivocally shown that marked differences in rates prevail, and that these relate to certain habits of living and lifestyle-related risk factors common in some populations and rare in others. Epidemiologic investigations within the United States have confirmed that susceptibility to CHD and the other major cardiovascular diseases is related to several traits, designated major risk factors because of their frequency in the population, their strong independent impact on proneness to the disease, and their potential amenability to prevention and control. In particular, these international and national research efforts have yielded extensive information on the roles of high fat diet, hypercholesterolemia, hypertension, and cigarette smoking. Evidence is also available indicating that sedentary habits, obesity, clinical diabetes, and Type A behavior pattern contribute independently to risk.

The extensive findings of these long-term population studies have served as the basis for major randomized controlled trials--currently in progress--to assess the ability to reduce the impact of the major cardiovascular diseases by controlling the key risk factors in high-risk individuals. These findings also form the basis for the few pilot community demonstration projects in this area undertaken thus far, as well as for efforts throughout the population--for example, the National High Blood Pressure Education Program--aimed at making available new knowledge to the health professions and the public as quickly and effectively as possible.

Thus, this period has witnessed every phase of development--from basic to applied research, to pilot demonstration control efforts, and to generalized application of valid knowledge in the community as a whole.

While the research effort has been extensive and its contributions important, certain major limitations need to be kept in focus if maximum advantage is to be taken of present opportunities. First and foremost, the data base is lacking for a comprehensive description and definitive elucidation of the reasons for the decline since 1968 in mortality from coronary heart disease and the other major cardiovascular diseases. Are these recent downward trends in mortality manifest uniformly throughout the adult population--for all regions and states, socioeconomic-racial-ethnic strata? If not, what are the key differentiating factors accounting for the differences? Do the decreases in mortality reflect falls in incidence rates of these diseases, i.e., declines in the rates of occurrence of both nonfatal and fatal events--a true overall decline in amount of these diseases (including heart attack) in the population and its various age-sex-race-ethnic-geographic-socioeconomic strata? Or alternately, are the declines in mortality largely a reflection of continuing very high incidence rates, but lower case fatality rates, i.e., a smaller proportion of deaths among people with the diseases? If the former alternative is the main reason for the declines, i.e., reduced incidence rates, why? Are they due to improved lifestyles in the nation, better patterns of eating, less smoking leading to improved status with respect to the major coronary risk factors (hypercholesterolemia, hypertension, cigarette smoking), more exercise with improved cardiopulmonary fitness, less obesity, less diabetes, all adding up to significant prevention of disease? What role is being played by the progress made in detection, evaluation, treatment, and control of the millions of people with high blood pressure? Alternatively, if lower case fatality rates are principally responsible for the declines in mortality, why the lower case fatality rates? Have the diseases become less severe? If so, why? Are modern treatments--emergency, acute, long-term--saving lives of those already ill? Answers to such key questions are needed as a scientific basis for sound public policy in the efforts to continue and intensify the present declines in mortality.

However, sound and comprehensive data on trends of morbidity from these diseases--i.e., on patterns of nonfatal as well as fatal disease--for major strata of the U.S. population have not been systematically collected. Correspondingly, standardized data on trends of lifestyles, environmental exposures, and risk factors have also not been systematically collected for representative samples of the population by age, sex, race, ethnic origin, geographic region, and socioeconomic level. Nor have systematic efforts been made as yet to relate patterns of change in lifestyles, environmental exposures, and risk factors in different segments of the population to patterns of change in incidence and mortality from CHD and the other major CV diseases. Filling these gaps is an urgent need, and a challenge in terms of the opportunity afforded by the fact of the declining mortality rates. Specifically, there is a need for an effective surveillance system to monitor trends of morbidity and mortality, and trends of lifestyles and risk factors, in order to assess the interrelationships between them, i.e., to evaluate whether improved lifestyle and improved control of risk factors (including control of hypertension by both nonpharmacologic and pharmacologic means) are significant contributors to the decline in mortality from CHD

and the other major CV diseases. There is a need concurrently to monitor trends of emergency, acute, and long-term care for persons ill with CHD and the other CV diseases, and to assess trends of prognosis for these patients, in order to evaluate whether evolving treatments are influencing prognosis, i.e., are important contributors to the decline in mortality.

Another important limitation in the available data base on the major cardiovascular diseases is that comprehensive findings are extant only for middle-aged white men. Most studies have not included white women, black men, or black women. Findings are also sparse for two periods of life decisive for the key primary prevention effort--during the first years of childhood and during adolescence, when critical habits are formed.

Correspondingly, and of great importance for a more profound understanding of the etiology of the disease and the role of risk factors and environmental components in accounting for patterns and trends of the disease, the data in hand do not reflect the diversity in conditions and circumstances of the U.S. population. This is true not only for age-sex-race, but also for the regions of the United States, the multiplicity of socioeconomic and ethnic strata, the extensive varieties of environmental exposures, and the complexities and arrays of modern lifestyle.

The recommendations presented in summary fashion in this chapter aim to overcome these gaps. The chapters that follow deal in detail with these challenges, and elaborate on the needs and rationale of the research opportunities and the consequent recommendations.

II. Summary of Recommendations

Recommendation 1: Community Surveillance

While CHD mortality rates now are declining for the entire U.S. adult population, risk is known to vary among different geographic areas and socioeconomic and ethnic groups. The study of future trends in heart disease mortality and morbidity in different strata of the population and areas of the country, and the relation of these trends to changes in lifestyles, environmental exposures, and biologic risk factors, should lead to a fuller understanding of the complex causation of this disease. To monitor trends of incidence of fatal and nonfatal CHD and its relation to changing risk factors, NHLBI should initiate prospective surveillance of the populations of 10 communities across the country.

Such a system should be carefully set up in relation to such considerations as: current levels of CHD and CVD mortality (i.e., low, medium, and high) and declines in mortality since 1968 (low, medium, and high); racial, ethnic, and socioeconomic variables; environmental exposures; adequacy of sample sizes for resolving critical questions of trends of incidence and their relation to trends of lifestyles, risk factors, and treatments; and standardization of methods of measurement. Answers should be systematically sought to the following key questions: How do the trends of mortality relate to trends of incidence of the major cardiovascular diseases? How do the trends of disease incidence and mortality relate to trends of the major risk factors ("rich" diet, serum cholesterol, cigarette smoking, and blood pressure)? of exercise? of weight? of alcohol use? of plasma

glucose? Since lifestyle changes in eating, drinking, smoking, and exercise have apparently been greater among better educated and more affluent people, is the mortality decline also greater among these strata (keeping in mind and controlling for the special problem of greater rates of hypertension among blacks and the effects of its improved treatment)? Since CHD death rates differ in different geographical areas, and possibly trends of decline in rates also differ among these areas, are evolving environmental factors playing a role--over and above trends in lifestyles, major risk factors, and medical care? Again, proper community surveillance techniques, with sound longitudinal sampling and measurement methods, can yield data relevant to these matters. Careful longitudinal monitoring of the situation among women, especially in relation to the Pill, cigarettes, and sociocultural factors (work, Type A-B, etc.) is needed. The impact of CPR programs, high intensity coronary care units, pacemakers, bypass surgery, new drugs, and other forms of coronary care must be ascertained as well.

To facilitate these studies, NHLBI should be in support of legislation to minimize legal impediments to population monitoring for heart disease while ensuring protection of individual privacy. Collaboration should be sought with the National Center for Health Statistics (NCHS), the Center for Disease Control (CDC), the National Cancer Institute (NCI), and other agencies currently supporting mortality and disease surveillance systems. For less frequent forms of heart disease (congenital and rheumatic heart disease and cardiomyopathies), regional reporting systems should be implemented utilizing the national network of clinical centers now treating heart disease in the young. Research into improved methods for systematically generating and testing new hypotheses from these surveillance systems should be encouraged. (See chapter 2, recommendations 1, 2, and 3; chapter 3, recommendations 5 and 7; chapter 5, recommendation 1.)

Recommendation 2: Longitudinal Studies

Evidence has been accumulating that predisposition to adverse heart disease risk factors may be set early in life by genetics, diet, and other aspects of modern lifestyles. Some risk factors such as obesity, hypertension, and hypercholesterolemia may be partially determined by genetic factors or habits which are formed in infancy and childhood. For most risk factors, major changes occur between adolescence and early middle age in both males and females. During this time, there are major changes in lifestyle and biological profiles. If the increase in risk factors could be prevented or detected early, then disease might be avoided later. Therefore, careful longitudinal studies, some starting at birth, others in adolescence, should be developed to determine the interplay between environmental and genetic factors leading to an increase in the risk factors prior to middle age. Such studies should examine:

- The distribution and natural development of risk factors in family units of varying geographic, socioeconomic, and ethnic backgrounds.
- The relationship of lifestyle changes, including diet and physical activity, to changes in the standard risk factors.
- The relationship of hormonal and other biologic changes occurring during puberty to risk factor changes in both sexes.

- The relationship of hormonal changes due to menstruation, pregnancy, oral contraceptive use, and menopause to risk factor changes in women.

Some of these studies should encompass black, Latins, and Native American populations. They should include efforts to elucidate the reasons for the now well-established inverse relationship between education and blood pressure in both whites and blacks. They should--in their evaluation of genetic precursors, risk factors, and social and environmental variables--encompass the entire age range.

These studies should be planned to last at least 5 years, and probably longer, to assure valid assessment of longitudinal trends and adequate baseline data for subsequent evaluation of long-term morbidity and mortality. Support should be provided to develop improved methods for studying familial effects and for assessing longitudinal trends in risk factor profiles. (See chapter 3, recommendations 4 and 6; chapter 6, recommendation 2.)

Recommendation 3: Salt

Clinical trials of the effects of reduced salt intake are needed in infants, children, and adults to assess the role of salt on blood pressure. These studies should be part of a comprehensive primary and secondary preventive effort, including assessment in randomized controlled trials of the effects of lower salt intake on blood pressure for those already hypertensive and for the hypertension-prone. The studies of salt intake should be linked with studies of weight reduction, so that confounding of these two interrelated variables is taken into account. (See chapter 3, recommendation 1.)

Recommendation 4: Physical Activity

Methods should be developed for the more precise measurement and description of physical activity and fitness in the general American population and in specific subgroups. These methods should be used to investigate the role of physical activity--its type, duration, frequency, and intensity--in controlling and preventing the emergence of CVD risk factors (for example, hyperlipidemia, obesity, diabetes, and high blood pressure) and cardiovascular diseases. (See chapter 3, recommendation 3; chapter 6, recommendation 1.)

Recommendation 5: Risk Factor Variability

Risk factor measurements usually have been obtained at rest in the environment of the medical clinic. There is need to determine the dynamic short-term changes in risk factors and behavior that occur during the challenges of daily life and the role of variability of risk factors as predictors and determinants of disease. Therefore, studies of dynamic changes over time in blood pressure, serum cholesterol, weight, activity, and smoking should be pursued. These studies should take into account the relationship of risk factor variability to:

- The behavioral characteristics of the individual (for example, Type A behavior pattern).
- The environmental situation (for example, at work, at home, and in the community).
- Neurohumoral and hormonal profiles of the individual.
- Subsequent risk of disease.

(See chapter 3, recommendation 3; chapter 6, recommendation 3.)

Recommendation 6: Occupational Exposures

Hypertensive and atherosclerotic diseases are common throughout the middle-aged and elderly population of the U.S., in all geographic-ethnic-racial-socioeconomic strata. Therefore, it is reasonable to infer that key causal factors are operative in the general macroenvironment, and not highly localized in specific microenvironments. Nevertheless, amidst this commonality of these endemic diseases, there are important differences in rates in different strata of the population. The reasons for these need to be explored, as a means of elucidating both etiologic mechanisms and improved approaches to control. In this context, specific micro-environmental exposures at the work place need to be studied, to assess whether--over and above broad lifestyle, risk factor, and environmental factors--specific physical and chemical exposures are important contributors to the high incidence of CHD (including sudden death) in industrialized nations. Investigations are needed to test specific hypotheses concerning the possible cardiovascular effects of relatively high exposures at work. Studies among occupational groups to determine the role of chemical and physical exposures in the etiology of hypertension, coronary heart disease, and sudden death are needed both on a nationwide basis and in specific localized industries with specific exposures hypothesized to be high risk. (See chapter 4, recommendation 3.)

Recommendation 7: Type A Behavior Pattern

Several studies have observed a strong relationship between Type A behavior pattern (TABP) and coronary heart disease. Further study of this behavior pattern is needed, with special emphasis on further prospective assessment of its role as a risk factor, its predictive power in various population groups, its determinants, and the biologic mechanisms possibly linking TABP to coronary atherosclerosis and its manifestations. (See chapter 4, recommendation 1.)

Recommendation 8: Social Change and Mobility

Higher rates of coronary heart disease have been observed among persons experiencing various types of life change and mobility. Further study is needed of persons experiencing social change, migration, and mobility, with particular emphasis on geographic and cultural groups known to exhibit different rates of CHD. Special focus should be given to the psychosocial and biologic mechanisms linking social change to CHD. (See chapter 4, recommendation 2.)

Recommendation 9: Cigarette Smoking

Major research efforts on the health aspects of smoking should continue, with the goal--through effective mass public education--of progressively reducing and eliminating this habit among Americans. There is a need for expanded health education programs aimed at influencing the rate at which people start and stop smoking cigarettes. Systematic sampling should be used to evaluate the effectiveness of these programs. Surveillance of smoking behavior nationally, regionally, and in major socioeconomic and ethnic strata should be continued and expanded to include objective measurements of smoking and dose. (See chapter 3, recommendation 2.)

Recommendation 10: Evaluation of Intervention Techniques

New treatments and new interventions are often introduced without adequate knowledge of their likely positive effects--or side effects. The common epidemiological methods of evaluating after-the-fact consequences need to be extended to assess the quality of medical practice and the value of interventions.

NHLBI should sponsor studies of the quality of cardiovascular medical care and the effects of intervention. Methodological developments should be carried out in cooperation with other agencies (for example, the National Cancer Institute) concerned with measuring the effects of intervention on arresting the development of chronic diseases. Such studies should evaluate the effectiveness of surgical intervention, including coronary bypass and congenital heart disease surgery, drug therapy such as the use of prostaglandin inhibitors or indomethacin in the management of patent ductus arteriosus in children, and behavioral techniques used in the prevention or therapy of coronary heart disease. There is also need for a workshop on preventive strategies for rheumatic fever and rheumatic heart disease in the current era. (See chapter 5, recommendations 2 and 3; chapter 6, recommendation 4.)

Recommendation 11: Water Hardness

The differences in CHD mortality rates reported in several studies between geographic areas differing in hardness of local water supplies remain to be validated and explained. Further studies are needed relating CHD and risk factor levels to exposure of individuals to components of drinking water such as magnesium, lead, cadmium, copper, and zinc. (See chapter 4, recommendation 4).

Recommendation 12: Training

NHLBI should expand educational programs in cooperation with epidemiology departments in schools of public health and with departments of preventive medicine in schools of medicine that have substantial strength in cardiovascular epidemiology. These educational programs should have the following characteristics:

- Training of both epidemiologists and biostatisticians.
- Stipends that are competitive with other training opportunities, sufficient to attract young M.D.'s as well as other postdoctoral and predoctoral candidates.
- Institutional support to the departments conducting the training programs for faculty and support staff.
- Arrangements for on-the-job training with Federal, state, and local agencies.
- Support extending over a 5-year period.

(See chapter 7.)

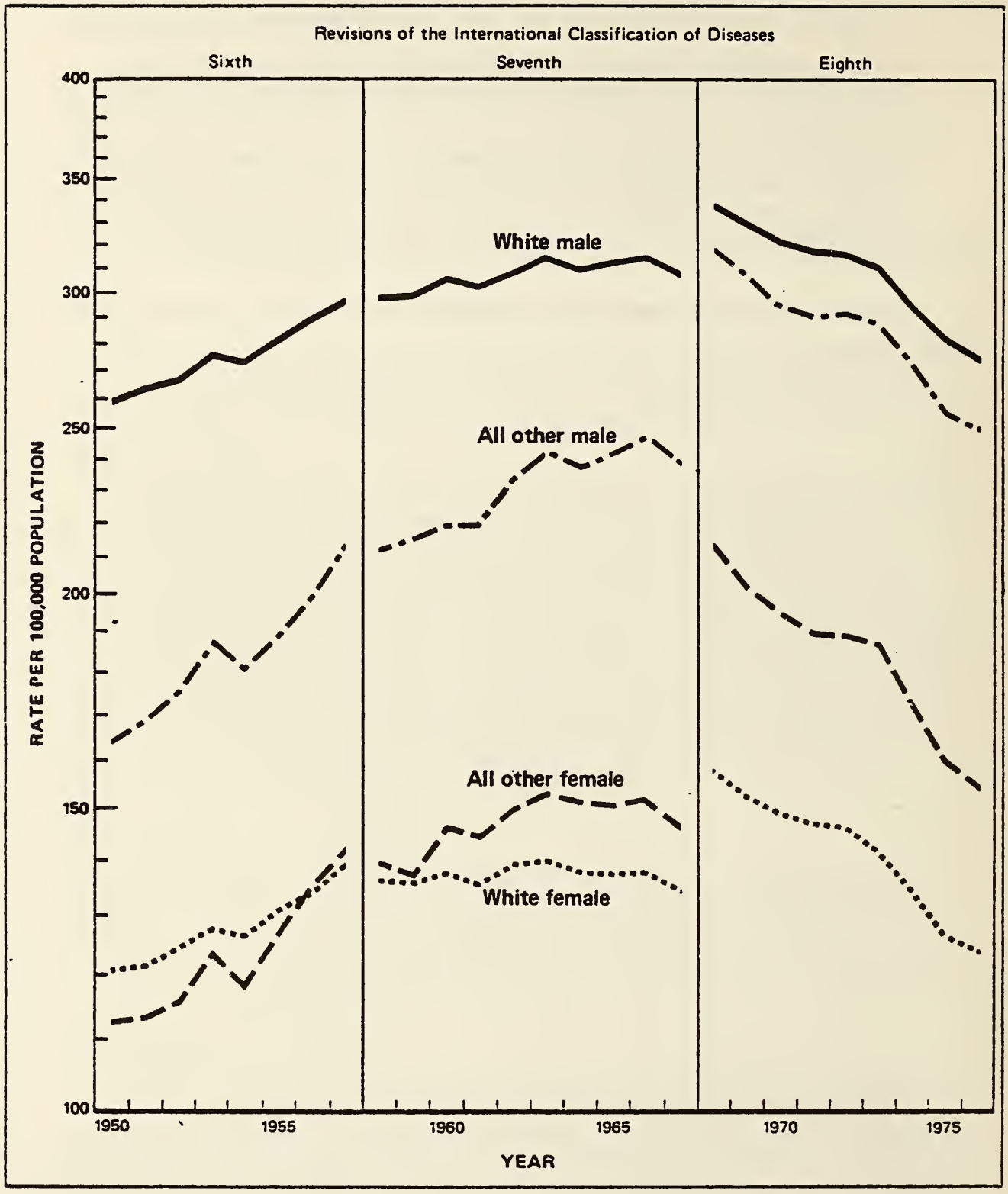

Figure 1. Age-adjusted death rates for ischemic heart disease, by color and sex: United States, 1950-76

Table 1

Percent change in mortality rates
United States, 1968 to 1976
persons age 15-74, by sex-color

CAUSE OF DEATH	PERCENT CHANGE, 1968 TO 1976, BY SEX–COLOR				
	WHITE MEN	WHITE WOMEN	NON-WHITE MEN	NON-WHITE WOMEN	ALL
CORONARY HEART DISEASE	–21.0	–26.5	–30.7	–39.1	–24.3
CEREBRO–VASCULAR DIS.	–30.6	–30.4	–43.7	–47.1	–32.7
MAJOR CV DISEASES	–20.9	–26.1	–33.2	–40.7	–24.6
ALL CAUSES	–15.3	–16.4	–24.8	–32.7	–17.3

Table 2

Percent change in CHD mortality 1940-1976
ages 35-74

SEX–COLOR	1940 TO 1948	1949 TO 1957	1958 TO 1967	1968 TO 1976
WHITE MALES	+14.9	+ 8.0	+ 2.3	–21.0
WHITE FEMALES	–3.3	+ 0.5	–7.3	–26.5
NON–WHITE MALES	+20.6	+18.7	+13.0	–30.7
NON–WHITE FEMALES	+15.7	+10.6	+ 3.8	–39.1

Surveillance of Heart Disease Mortality, Morbidity, and Risk Factors

I. Purposes of Surveillance

From current surveillance of heart disease, we know that even though the mortality from coronary heart disease has decreased in the United States, it remains the number one killer, accounting for about one-third of all deaths. Congenital heart diseases affect 8 of 1,000 live births, and two congenital heart diseases--patent ductus arteriosus (PDA) and ventricular septal defect (VSD)--have increased in recent years. Present investigations and surveillance systems have not adequately explained these time trends. Progress toward solving heart disease problems depends on developing and establishing better population data bases and performing appropriate epidemiologic analyses.

These observations highlight a major purpose of heart disease surveillance--evaluating the changing status of heart disease in the population. A second major purpose of new and improved surveillance is that of generating and testing hypotheses on the causes of heart disease. For example, why are there such marked geographic differentials in death rates for acute myocardial infarction?

Measures of morbidity (disease incidence, etc.) as well as mortality rates are needed for efficient surveillance. The lack of adequate national morbidity measures has become evident as the reasons for the mortality decline are examined in more detail. Thus, given the inadequacy of morbidity data, it is not possible to ascertain definitively whether the decline in mortality reflects a true fall in overall incidence of the disease or a decrease in the case fatality rate.

It is also extremely useful to have the known and suspected risk factors for heart disease under surveillance. What are the trends in smoking nationally, regionally, and in major socioeconomic and ethnic strata? in fat consumption and lipid levels? in weight and physical activity? in blood pressure? Do observed changes in these factors relate to changes in heart disease morbidity? A better and more systematic surveillance would provide answers to these questions, but our present systems do not allow such determinations.

The remainder of this chapter describes the present surveillance and monitoring programs, indicates where improvements should be made, and describes the most pressing research areas in heart disease surveillance.

II. Current Major Programs

A. United States

1. Mortality

The Mortality Branch of the National Center for Health Statistics' (NCHS) Division of Vital Statistics annually receives and collates death records from all 50 states and from New York City and the District of

Columbia. There are nearly 2 million deaths each year in the United States, and approximately half of these deaths are attributed to cardiovascular disease. NCHS produces annual volumes and tapes containing mortality data. In addition, NCHS is investigating the feasibility of systematically displaying maps of age-specific and age-adjusted mortality rates by race and sex groups so as to detect unusual patterns and trends by geographic regions for most major causes of death. Such data have been used in the NHLBI Mapping Project to relate heart disease death rates to social and economic indices.

2. Morbidity and Risk Factors

a. National Surveys. The National Center for Health Statistics conducts periodic health surveys to estimate morbidity levels and many other factors related to health. The Health Interview Survey (HIS) contacts about 40,000 households (140,000 persons) annually and, using trained health interviewers, obtains information on self-perceived health habits.

The Health and Nutrition Examination Surveys (HANES) are conducted in cycles completed every 4 years. Approximately 20,000 persons, selected in a national probability sample, are given a full set of medical and other examinations by physicians and other health professionals in a standardized examination format.

The Hospital Discharge Survey is an annual probability sample of information obtained from abstracts of hospital discharge data selected from short-stay U.S. hospitals.

b. Community Studies. In addition to these national surveys, certain community-based and cohort studies provide significant additions to the monitoring of heart disease morbidity and risk factors.

The National Heart, Lung, and Blood Institute is currently sponsoring a number of such population-based studies. Three adult groups are being followed for morbidity and mortality outcomes in Framingham, Mass.; Honolulu, Hawaii; and urban and rural areas in Puerto Rico. Risk factors and differing cultural effects are being determined, but the populations are not large enough or representative enough to provide accurate information on heart disease trends over time. Pooling of such data with other cohort studies in Chicago, Ill., Albany, N.Y., Tecumseh, Mich., and Los Angeles, Calif., has provided a better understanding of the relationship of risk factors and heart disease outcomes.

The frequency and natural development of risk factors in school children are presently being studied in NHLBI-sponsored Specialized Centers of Research in Muscatine, Iowa, and Bogalusa, La. Such surveillance will lead to estimates of changes in risk factors with time and possibly suggest etiologic reasons for differences in adult levels of risk factors. A different type of surveillance is occurring in Orleans Parish, La. Specialized pathological studies for extent of atherosclerosis are being performed on tissues from deaths occurring in young men. Such observations may provide information on whether the frequency and extent of atherosclerosis is changing over time.

The Lipid Research Clinics Program involves two components. Lipoprotein predictors of disease, including high density lipoprotein, are being ascertained in 12 U.S. and 3 foreign populations. In addition, the potential beneficial effect of lowering cholesterol is being studied. NHLBI is involved with a number of other specialized clinical trials involving primary prevention of CHD, stroke, and heart and renal failure by blood pressure reduction (Hypertension Detection and Followup Program) and multiple risk factor modification (Multiple Risk Factor Intervention Trial), and secondary prevention in individuals with known heart disease by agents such as aspirin (Aspirin Myocardial Infarction Trial) antiarrhythmic drugs (Beta-Blocker Heart Attack Trial), and by surgery in the Coronary Artery Surgery Trial. Such intervention studies, however, provide limited surveillance information, since even the control groups change their behavior patterns or risk factors by participation in the study.

Besides formal clinical trials, a series of demonstration intervention projects are currently sponsored by NHLBI. They include a component of surveillance for cardiovascular disease and/or risk factors in an effort to determine the impact of the intervention. The Baylor Research and Demonstration Center has surveyed Houston adolescents for smoking habits through the school system. An intervention program will be used with a subset in order to determine whether the frequency of smoking behavior is changing. In a project coordinated by Stanford University, a selected group of communities in California will be monitored for cardiovascular disease, and a program for intervention on major risk factors will be implemented and the community impact on disease assessed. On a larger scale, four states--Connecticut, Maryland, California, and South Carolina--are currently determining cardiovascular disease mortality and monitoring hospital discharges for relevant diseases in order to ascertain the impact of statewide coordinated hypertensive therapy programs. Although each of these studies attempts to use surveillance, none has a comprehensive system that can be reliably depended on to give definitive and generalizable information on documented sudden and unexpected deaths and nonfatal heart attack incidence over time.

c. **Congenital Heart Disease.** The incidence (newborn prevalence) of congenital heart disease is measured in the various CDC-affiliated programs that monitor the incidence of birth defects. Newborn nursery discharge diagnoses monitor the incidence of birth defects occurring in one-third of the nation's births. These data, however, are deficient for congenital heart disease diagnosed after the first week of life. A separate surveillance system is maintained in metropolitan Atlanta, where more intensive studies and followup are available. This center assists two states (Florida and Nebraska) with surveillance activities. In large measure, the incidence of congenital heart disease has remained stable. In contrast, the incidence of patent ductus arteriosus has tripled and the incidence of ventricular septal defect has doubled over recent years. An informal international Clearinghouse of Birth Defects Monitoring Programs has been supported by the National Foundation-March of Dimes, for several years. The purpose is to promote an exchange of information among the centers that monitor birth defects. Each of the monitoring centers follows the incidence of one or more congenital heart diseases. The World Health Organization (WHO) is exploring a more formal program with similar objectives.

B. International

The World Health Organization provides international mortality data and publishes cause-specific mortality tables for participating countries. Such publications use International Classification of Diseases (Adapted) codes, but there is no attempt to validate diagnoses.

Within certain countries (for example, Sweden, Finland, and Germany), specific geographic areas maintain myocardial infarction registries, which attempt to tabulate all heart attack cases, both nonfatal and fatal. Such registries can be used for trend data and can be compared with data on potential risk factors. Various casefinding and preventive programs have been established by countries. Recently results from the north Karelia, Finland, study suggest that risk factor modification may have an effect on heart disease outcome. At present, WHO is sponsoring a protocol for studies on school-age children of the determinants of atherosclerosis in countries with differing cultural and socioeconomic characteristics.

III. A Comprehensive Monitoring System

Much more extensive, periodic, and systematic sampling of the onset and recurrence of heart disease in the U.S. population--and of lifestyle patterns and other possibly related traits--would be extremely useful. In this way, a detailed assessment of changes in the patterns of heart disease in the U.S. population and the causes of these changes would be possible. Assessment of trends and other comparisons concerning the incidence of heart diseases is also critically needed.

An effective comprehensive monitoring system for heart disease would have built-in quality control mechanisms to assure classification comparability at a reasonable level. Researchers need to be confident that when geographic and other differentials are noted, the differences are not attributable to assignment of different labels to similar pathologic phenomena.

For similar reasons, measurements of exposure to risk factors need to be comparable. Quality control of a monitoring system for such things as serum cholesterol, smoking, and blood pressure and attempts at monitoring more elusive factors such as nutrition, stress, pollution exposures, physical activity, and other health habits are mandatory to assess their effects on disease.

IV. Major Research Problems and Opportunities

Present surveys are inadequate for many important evaluations and study purposes. There are many research opportunities that could be seized with a cost-efficient surveillance system for heart disease morbidity and risk factors. These are described in the following sections.

A. Heart Disease Trends

Further investigation into the decline in cardiovascular disease mortality and its determinants and identification of those subpopulations experiencing greater decreases are needed to gain insight into the processes responsible for this important phenomenon. This includes investigations distinguishing between declining case mortality rates and declining incidence rates as partial or joint determinants of the decrease. Similar attention should be directed toward areas demonstrating an increase in heart disease rates.

There is a specific need for an effective system, similar to the European myocardial infarction registries, to monitor morbidity and mortality trends. Such a system should be carefully set up in relation to sections of the country and to racial, ethnic, and socioeconomic variables. How do these trends relate to trends of the major risk factors ("rich" diet, serum cholesterol, cigarette smoking, and blood pressure)? of exercise? of weight? Since lifestyle changes in diet, smoking, and exercise have apparently been greater among better educated and more affluent people, is the mortality decline also greater among these strata (keeping in mind and controlling for the special problem of greater rates of hypertension among blacks, especially poor blacks, and the effects of its improved treatment)? Again, proper community surveillance techniques, with sound longitudinal sampling and measurement methods, can yield data relevant to this matter. Careful longitudinal monitoring of the situation among women, especially in relation to the Pill, cigarettes, and sociocultural factors (work, Type A-B, etc.) is needed. Why are rates for blacks declining even more than for whites, especially for black women? Is this because of hypertension treatment? The impact of high intensity coronary care units, pacemakers, bypass surgery, new drugs, and other forms of coronary care must be ascertained as well.

B. Geographic and International Heart Disease Differences

Within the United States, there are unexplained regional differences in coronary and stroke mortality. In addition, sizable differences exist in the prevalence of and mortality from hypertensive disease in different regions and locales (for example, high rates in the Southeast and South Central states). Further examination of such differences should be encouraged. There may be correlations with noncardiovascular diseases, such as cancer--perhaps a common etiological basis in nutritional factors and trace metals, for example. The "macroenvironment" (involving population density, residential, and meteorological factors) certainly differs with geography, and such external forces could contribute to geographic differences.

Exceptionally low rates of hypertension and coronary disease are found in several areas outside the continental United States. Indeed, there are still populations in the world with little or no hypertension. The testing seems warranted of specific hypotheses as to the reasons for this (including not only Polynesian and other Pacific populations, but also populations in Africa and the Western Hemisphere--for example, Amazonian and Mexican Indians), and reasons for contrasts between these populations and those with an unusually high prevalence of hypertension (for example, among poor blacks in counties of the Southern United States).

Another important question is whether the high rate of CHD in Framingham (and elsewhere in the United States), compared with that of Yugoslavia, Puerto Rico, and Honolulu, is due to gross dietary differences--for example, dietary lipids, proteins, sugar, fiber, magnesium deficiency, imbalance in trace element nutrition, or other factors. A possible approach would involve the collection of duplicate diets (including water samples) for adequate time periods from samples of persons for accurate analysis for macronutrients and micronutrients (including magnesium, copper, zinc, lead, and cadmium).

Studies involving migrants to and from high or low disease areas within the United States and immigrants between international areas and the United States can be of value in understanding the known geographic differences. For example, studies of migration (rural and urban, Southern blacks to the urban North, Appalachian whites to the urban North, Asians or Europeans to the United States, or Latin Americans from Puerto Rico, Cuba, and Mexico to U.S. cities) might reveal patterns of hypertension in migrants compared with nonmigrant groups and reasons for the differences. Because of the known black-white differences in the United States, studies of African blacks, both in their native countries and after migration, could provide valuable information.

C. Population Surveillance

Studies of heart disease trends, geographic and international differences, and risk factor changes require careful monitoring of appropriate population samples. Periodic followup of the HANES (NCHS) survey cohort is one possibility. Improved prognostic formulas and risk factor assessments would be one objective; another would be detection of new potential risk factors. Another approach would be the surveillance of selected communities to enumerate fatal and nonfatal events. About 10 stable communities of 100,000 to 300,000 people should offer sufficient registration areas for such a purpose. The degree to which such communities relate to the whole nation could be ascertained by comparing their disease experience with the national survey figures. The National Cancer Institute has used such a model in its Surveillance, Epidemiology, and End Results (SEER) program. Possible studies of the impact of mass participation in various lifestyle change programs (weight loss, jogging, tennis, shopping in health food stores, quitting cigarettes, etc.) could be undertaken. This might involve the need to develop measures to be used at the community level as an indication of individual attributes. A combination of community and national surveillance would allow the collection of unique information, such as the impact of the results of current NHLBI clinical trials.

D. Surveillance Methodology

Research is needed on how to design efficient systems of surveillance. In addition, improved methods for analyzing surveillance data are needed. What constitutes a statistically noteworthy change (as detected by the various available measurements) in the dynamic process of heart disease that affects a changing population? How are such changes most easily detected?

In the same manner, can new methods be developed to uncover new leads or new hypotheses by systematic examination of community surveillance or individual data files?

Basic to the needs of surveillance is the removal of unnecessary legal impediments to scientific investigation. The epidemiologic community must remain alert to the development of such legislation.

Other surveillance issues needing attention are:

- The feasibility of conducting longitudinal (matching) studies emphasizing the relationships between occupation and heart disease.
- The effect of the decline in autopsy rate on the quality of mortality surveillance.
- Developing the capability within NHLBI to respond to perceived new potential epidemics of heart disease (congenital, ischemic, and otherwise).
- Comparing heart disease trends with those of other countries and the comparability of the information, including comparability of exposure data.
- The feasibility of establishing a central repository of data gathered from various population studies NHLBI currently supports. These data have the potential for important longitudinal analyses by expanding data bases and allowing analyses of questions not answerable from individual small data banks. In addition, NHLBI should help interested and qualified investigators to utilize these large data bases.

E. Collaboration with Other Agencies

In most instances, it would not be efficient to embark on large-scale population studies with surveillance of only one disease in mind. Collaboration with other agencies will be required. NHLBI should initiate the coordination of such studies with agencies such as NCHS, CDC, and NCI.

Some examples are:

- Collaborate with NCHS on developing a periodic followup of the HANES cohort. This group is the only national probability sample that has had a complete standardized medical examination.
- Collaborate with the Social Security Administration to develop methods for using its data file for epidemiologic studies while providing privacy protection.
- Coordinate with the Environmental Protection Agency and National Institute of Occupational Safety and Health to investigate the epidemiologic utility of matching data bases of varying types at the community level, for example, local chemical exposures and mortality rates.

- Coordinate (measurement standardization, etc.) community studies with national surveys (HIS, HANES, etc.) to study and understand regional and interpersonal comparisons.

- Collaborate with the Bureau of the Census to incorporate questions on heart disease and risk factors in a sampling of the probable 1985 census. In addition to providing unique baseline population information, these data would allow evaluation of important aspects of community studies and national surveys.

- Collaborate with NCHS on redesigning the national health surveys, including the hospital discharge and health interview surveys, to produce improved estimates of heart disease and modifiable risk factor prevalence in small geographic areas as well as for the nation.

Recommendations

1. Although the mortality rates from coronary heart disease have been declining steadily during the past 15 years in the United States, this still remains the number one killer, accounting for more than one-third of all deaths. Present investigations and surveillance systems have not adequately explained these trends. In particular, the lack of adequate national measures of morbidity (incidence of disease, nonfatal disease) has become evident as the reasons for the mortality decline are examined in more detail. Thus, given the inadequacy of morbidity data, it is not possible to ascertain definitively whether the decline in mortality reflects a true fall in the occurrence of heart disease or a decrease in the case fatality rate (i.e., improved survival of those with disease). The study of future trends in heart disease mortality and morbidity in different strata of the population and areas of the country, and the relation of these trends to changes in lifestyles, environmental exposures, and biologic risk factors, should also lead to a fuller understanding of the complex causation of this disease. Therefore, to monitor trends of incidence of fatal and nonfatal CHD and its relation to changing risk factors, NHLBI should initiate prospective surveillance of the populations of 10 communities across the country.

   Such a system should be carefully set up in relation to such considerations as: current levels of CHD and CVD mortality (i.e., low, medium, and high) and declines in mortality since 1968 (low, medium, and high); racial, ethnic, and socioeconomic variables; environmental exposures; adequacy of sample sizes for resolving critical questions of trends of incidence and their relation to trends of lifestyles, risk factors, and treatments; and standardization of methods of measurement. Answers should be systematically sought to the following key questions: How do the trends of mortality relate to trends of incidence of the major cardiovascular diseases? How do the trends of disease incidence and mortality relate to trends of the major risk factors ("rich" diet, serum cholesterol, cigarette smoking, and blood pressure)? of exercise? of weight? of alcohol use? of plasma glucose? Since lifestyle changes in eating, drinking, smoking, and exercise have apparently been greater among better educated and more affluent people, is the mortality decline also greater among these strata (keeping in mind and controlling for the special problem of greater rates of hypertension among blacks and the effects of its improved treatment)? Since CHD death rates differ in different geographical areas, and possibly trends of decline in rates also differ among these areas, are evolving environmental factors playing a role--over and above trends in lifestyles, major risk factors, and medical care? Again, proper community surveillance techniques, with sound longitudinal sampling and measurement methods, can yield data relevant to these matters. Careful longitudinal monitoring of the situation among women, especially in relation to the Pill, cigarettes, and sociocultural factors (work, Type A-B, etc.) is needed. The impact of CPR programs, high intensity coronary care units, pacemakers, bypass surgery, new drugs, and other forms of coronary care units, must be ascertained as well.

2. Because the Privacy Act has significantly hampered epidemiologic research on heart and other diseases, NHLBI should aggressively seek legislation that minimizes legal impediments to population monitoring for diseases while ensuring individual privacy protection.

3. To profit maximally from surveillance techniques, NHLBI should encourage research on the best methods for systematically developing and testing new hypotheses from routine heart (and other) disease surveillance systems. An example would be identifying groups of persons or communities with unusual rates of heart disease. The characterization of such groups by a combination of many variables such as locale, altitude, environmental and sociocultural factors, etc., may yield new hypotheses that could be tested in separate studies.

Risk Factors

This chapter is concerned with research on key risk factors for the major cardiovascular diseases, i.e., nutrition, serum lipids, lipoproteins, blood pressure, cigarette smoking, and physical activity. It emphasizes the need and importance of population studies of particular age-sex-race-ethnic groups and geographic areas, as well as investigations of risk factor-disease trends over time. It calls attention to the need and importance of using the family as a unit for study of the interplay between environmental and genetic factors.

Blood clotting factors are also considered.

I. Epidemiologic Patterns of the Key Risk Factors

A. Age Patterns

Major risk factors need to be studied over the age span of individuals and populations. There is a particular need for prospective studies to evaluate further the relationship between the risk factors measured during childhood and subsequent levels during adult years. Most of the information to date on age trends has been cross-sectional, that is, determination at one point in time of the levels of risk factors in groups of people of various ages. Of particular concern are the critical periods early in childhood, and between adolescence and young adult life (from ages 12 to 40), periods when habit patterns and many risk factors are decisively and dynamically influenced, including diet, physical activity, blood pressure, serum cholesterol, weight, and blood sugar. If the rise of risk factors between adolescence and young adult life could be obviated, many of the subsequent diseases of adult life, especially coronary heart disease and stroke, might be prevented.

The first 5 years of life is a critical age span, especially with regard to lipid metabolism. The change is greatest in lipoproteins during the first few months of life. A particular concern to investigators are the effects of breast versus bottle feeding, and the composition of the formula, on subsequent lipoprotein levels during childhood and into the adult years. The long-term consequences of infant feeding practices on obesity in later childhood and adult obesity require study, as does the effect of salt intake during infancy on long-term salt preference and patterns of development of hypertension in later life.

The consistency of risk factor levels in children through adolescence to adulthood needs further evaluation. Most studies have followed children for a relatively short time. Some have noted what is called "tracking," that is, children with the highest levels tend to remain high and those with low levels tend to remain low. If the concept of tracking holds into the adult years, then strategically it may be more valuable to give major emphasis to identification of high-risk children and seek to prevent their development of high-risk factors as a primary prevention measure. On the other hand, if tracking is inconsequential, then the determination and modification of risk factors in selected children may deserve less attention, and interventions based on mass sociocultural influences will be the central public health emphasis.

A key factor in the period from ages 12 to 40 appears to be weight gain. How weight gain relates to the interplay among dietary change, decreased physical activity, and hormonal patterns needs to be evaluated for individuals and cultural groups. Also the relationship of weight change to the increase in levels of the risk factors during this age span should be determined. The causes of changes in lifestyle during this period should be better delineated, including occupational change, geographic mobility, and marital status.

At the other end of the age spectrum, the situation among the elderly has received little research attention. Little is known about the distribution of risk factors, their changes, and their relative importance in this older stratum of the population. The apparent decrease in weight found in cross-sectional data in older people should be verified by longitudinal studies, and the reasons for the weight change evaluated. The importance of elevated risk factors, especially blood pressure, lipoprotein fractions, and blood glucose, needs to be explored in the older age segment in relationship to a major disease of the elderly, stroke. The treatment of older people to reduce blood pressure and other factors requires trials to determine the benefits of treatment against potential hazards.

B. Racial and Ethnic Patterns

The distribution of major risk factors in select populations with known or potentially unusual characteristics should be determined. Investigation of populations with unique characteristics may significantly enhance our knowledge of the relationship between risk factors and disease. This also may yield a better understanding about the environmental and genetic determinants of these risk factors. For example, the apparent high prevalence of obesity, hypertriglyceridemia, and possibly hypertension among Mexican-Americans, with apparently low arteriosclerotic heart disease death rates, should be further evaluated. The high prevalence of diabetes among American Indians has been noted on several occasions. Research should continue in this area in relationship to cardiovascular disease risk. Black women have an inordinately high prevalence of obesity and hypertension. There are sizable differences in distributions of lipoproteins between blacks and whites, but relatively little information about the relationship of lipoprotein levels to risk of disease in the black population. Blacks have consistently higher blood pressure than whites and much higher mortality and incidence of stroke, while the reasons for their elevated blood pressure have been insufficiently explored. Longitudinal studies are needed of the risk of disease within black populations, especially in relation to blood pressure, blood sugar, and lipoprotein distributions.

C. Patterns of Geographic Distribution

Major risk factors and their trends should be determined in contrasting U.S. communities with high and low cardiovascular mortality rates, respectively. The few previous studies in communities with very divergent cardiovascular and cerebrovascular death rates were based on small sample sizes and did not include lipoprotein distributions or repeat determinations of blood pressure. Divergent rates of disease may be an important clue to other risk factors, especially environmental ones.

D. Patterns of Sex Differences

Women have much lower coronary heart disease death rates than men. Further investigation of the distribution of risk in relationship to sexual maturation, hormonal profiles, and obstetrical and menstrual history among women is needed to learn more about the sex differences in risk. Specific studies should include evaluation of the influences of exogenous hormones, problems of sexual maturation, the effects of artificial menopause, and variations of lipoprotein levels in relationship to the menstrual cycle. The recent experimental evidence that vasectomy in male nonhuman primates may aggravate diet-induced atherogenesis indicates the need for studies in the human population. The increase in blood cholesterol, blood pressure, and blood sugar among women after the age of 45-50 should be investigated in relation to the menopause, dietary factors, and activity levels. The remarkable difference in the trends of lipoprotein and blood pressure levels between men and women after age 50 (with women showing a substantial increase) may be an important clue to the relationship among hormones, aging, risk factors, and cardiovascular disease.

E. Temporal Patterns

Little information exists about trends in the distribution of risk factors in the U.S. population, despite obvious changes in the economy, in lifestyle, in dietary preferences, in physical activity levels, etc. Moreover, the reasons for the real decline in cardiovascular mortality remain undetermined, and primarily because of inadequate data, it is uncertain whether changes in any of these risk factors can account for the decrease.

Stroke rates have been declining for many years, starting prior to utilization of antihypertensive drugs. Unfortunately, there are practically no data on secular trends in the distribution of blood pressure, the prime risk factor for stroke. If the mean blood pressure is declining or if severe hypertension is disappearing, then the reasons should be investigated. Changes in blood pressure may be related to environmental, including nutritional, factors. Even data on the secular trends of height and weight are limited. Careful standardization of survey studies is needed to provide useful trend data.

II. Genetic Influences on the Key Risk Factors

A better understanding is needed of the genetic contribution to the distribution of risk factors. Further delineation is needed of monogenetic influences (e.g., familial hyperbetalipoproteinemia), genetic markers (e.g., HLA typing in relationship to lipoprotein levels, blood pressure, and blood sugar), and of specific apoproteins of lipoproteins. The work of the Lipid Research Clinics Program, Framingham offspring, and NHLBI twin studies, et al., should continue. The Framingham offspring study should be extended to include three generations. Studies of blood pressure in the young, including the pediatrics SCOR-A programs, may also increase understanding of genetic and environmental interactions.

A. Genetic-Environmental Interactions

Studies linking environmental, sociocultural, and genetic analyses should include a more detailed evaluation of the interactive relationships with the established risk factors. Racial differences in the distribution of biochemical measures in hypertension should be explored further for interaction of genetic and environmental factors. Likewise, distributions of HLA types should be assessed in regard to their comparative patterns of blood glucose, cholesterol, and blood pressure.

B. Premature Disease

Studies of young patients with stroke or heart attack are desirable. Many of these individuals will have major monogenetic hyperlipoproteinemia or abnormally high risk factors as a result of strong environmental or genetic influences. Some, however, may exhibit an acceleration of disease in response to "usual" levels of risk factors. Identification of such individuals and detailed family studies using genetic markers are needed. There may also be a genetic component to "cardiac fitness and work capacity." Individuals with poor cardiac fitness may have a greater risk of heart attack given the same degree of underlying atherosclerosis.

C. Other Genetic Studies

Other genetic studies are needed as follows:

1. Family studies of risk factors at "critical" times of life, including infancy, adolescence, and young adulthood, in different strata of the population.

2. Risk factor studies in special family relationships including twins, half-siblings, and foster or adopted children.

3. Continued studies of major or monogenic effects, including the severe hyperlipoproteinemias, and genetic markers such as human leukocyte antigens and their relationship to diabetes mellitus.

4. Detailed genetic studies of the protein fractions of plasma lipoproteins (apoproteins).

5. Genetic studies of individual responses to drug, dietary, or exercise therapy.

III. Lifestyle Traits

A. Nutrition and Eating Patterns

Nutrition and eating patterns play a major role in accounting for the population distribution of several cardiovascular risk factors. As already noted, it is important to investigate the relationship between feeding practices during the first year of life and blood lipoprotein levels. Thus, studies are needed on the influence of breast versus bottle feeding on subsequent changes in lipoprotein levels. Better methods of measuring

activity and diet are needed. The determinants of specific eating and exercise patterns should be investigated, including the social and physical environment. Experimental studies and demonstrations are needed to measure the effectiveness of health education programs that attempt to modify major risk factors (especially obesity, exercise, and dietary preferences) in children, adolescents, and adults.

More information is needed on the role of dietary fats and other dietary factors (fibers, trace elements, vegetable compared to animal protein) which may influence blood lipids. Controlled epidemiological and experimental studies are needed of these effects, including metabolic ward studies of the type done by Keys, Hegsted, Connor, Mattson, and their colleagues. Situations in which healthy individuals can be carefully monitored over several weeks to months should be brought into being, with special facilities where individuals can receive all meals and snacks while leading normal activities. Controlled studies should include assessments of interactions among specific host characteristics, specific behavioral types, and specific traits (e.g., obesity and leanness). Studies are needed of effects of diet composition in and out of caloric balance.

Alcohol intake is a major component of the American diet, and the relationship between alcohol intake, risk factors and disease needs much further study. Acutely, sizable alcohol intake raises triglyceride levels and VLDL cholesterol. It also is associated with higher levels of HDL cholesterol. Whether this latter finding is due to alcohol per se and is "protective" are unknown. Alcohol intake is also highly correlated with cigarette smoking. The effects of either of these variables on each other, especially in relationship to modification of these and other risk factors, need to be explored. Alcohol's effects on blood pressure and glucose metabolism need to be thoroughly evaluated. The physiological basis of the increase in blood pressure with heavy drinking, and the proportion of the population susceptible to this effect, should be determined.

Regular but low consumption of alcohol may be associated with a lower risk of heart attack, although the limited findings to date are not consistent on this matter. High doses, on the other hand, are associated with an excess mortality overall. Further studies are necessary to determine whether this low dose effect is real.

Nutritional factors may play a major role in the determination of blood pressure levels. Recently, potassium and possibly calcium intake have been investigated as determinants of blood pressure. The relation of salt intake to elevated blood pressure needs much further study in man. Very large intakes (e.g., in northern Japan) are associated with high prevalence rates of adult hypertension. However, whether a moderate decrease in the average salt intake in the United States will prevent and control high blood pressure has not been determined. Clinical trials make it possible to answer this question, while considering confounding factors of potassium, calcium, and weight loss, all of which may reduce blood pressure and modify the effects of sodium intake.

It is still not clear why caloric excess and obesity are associated with greater risk of high blood pressure. Furthermore, the relationship of weight change at different ages to change in blood pressure has not been

fully evaluated. For example, do obese children who become obese adults have the same risk of elevated blood pressure as adults who become obese after adolescence? Because many obese individuals do not develop significant adult hypertension, it would be worthwhile to measure the host susceptibility factors of obesity-related elevated blood pressure.

Further work is needed on the long-term natural history of elevated blood pressure in the obese and nonobese, as well as research on the efficacy of preventive and therapeutic measures, nonpharmacological and pharmacological. Information from large clinical trials such as HDFP and MRFIT should be exploited to explore these important questions. Also it is important to determine pathophysiological differences between obese and nonobese hypertensives in relation to salt metabolism and such biochemical measures as renin.

The role of weight reduction programs and drugs to modify blood pressure and reduce risk of disease for obese hypertensives should be put to a careful test. Whether blood pressure is best lowered by caloric restriction with and without salt reduction should be further evaluated.

Caloric excess as a critical determinant of blood sugar levels in adults should be further explored. New methods of evaluating blood glucose levels--e.g., using glycosylated hemoglobin--should be sought to increase understanding of the determinants of blood glucose and its variations. Further work is needed on the interrelationships among nutrition (quality and quantity), blood glucose, its regulatory hormones (insulin, glucagon, et al.), clinical diabetes, and risks for adults (male and female) of hypertension, CHD, stroke, and peripheral vascular disease. This remains an important and complex set of problems that need resolution.

The interrelationship between physical activity, calories, quantitative and qualitative measures of fatness, and overweight should be further investigated to explain reported social class gradients in blood pressure, stroke, and diabetes among black women, and diabetes among Mexican-Americans. The probable consequences of obesity--including elevated blood pressure, blood sugar, and lipids--require controlled studies of treatment in terms of reduction of weight, decrease in risk factors, and their effect on incidence of disease.

B. Cigarette Smoking

Major research efforts should continue with the goal to reduce the prevalence of cigarette smoking in the population. The evaluation of different types of cigarette smoking in relationship to carboxyhemoglobin levels, tar and nicotine, etc., and disease should proceed. Practical methods of quantifying smoking behavior (carboxyhemoglobin, thiocyanate, measurement of nicotine) should be refined and used, along with subjective measures to record smoking history (e.g., number of packs smoked, type of cigarette, inhalation characteristics). Objective measures of cigarette smoking are needed as possible better indicators or predictors of subsequent disease than the subjective smoking history. Cigar and pipe smoking need to be further evaluated as risk factors, as well as inhalation characteristics (as in individuals who have smoked only cigars or pipes). Risk relationships should be determined separately for these two groups by use of objective measures of dose.

Continued evaluation is needed of the health effects of changing tar, nicotine, and carbon monoxide content of cigarettes. The largest attributable risk for cigarette smoking is heart attack. Thus, studies that evaluate risk reduction should include heart attacks, as well as cancer rates.

Educational programs leading to a reduction of cigarette smoking and the prevention of smoking by children deserve high priority. Programs should be developed to evaluate the efficacy of various prevention strategies.

C. Physical Activity

The beneficial effects of regular physical activity on cardiovascular fitness and physical and mental well-being are well established. More data are needed on its possible salutary effects on blood pressure, serum cholesterol, blood sugar, and obesity. Epidemiologic data suggest that rhythmic (isotonic) exercise reduces the incidence, defers the onset, and diminishes the severity of CHD. But in the United States, "laborsaving" devices are prevalent at home and at the worksite. Regular physical activity at work continues to diminish, while it is probably increasing in leisure. These observations in the context of the beneficial effects of exercise suggest research needs in several areas. For example, as noted above, what is the effect of physical activity on glucose tolerance, insulin activity, blood pressure, blood lipids, and obesity? What is the frequency, duration, and intensity of activity necessary to achieve given levels of "beneficial" effect? Methods to measure physical activity and fitness and their biochemical and physiological effects are needed to supplement self-reports. Questionnaire and diary methods for collecting data on activity patterns need further assessment and refinement. Specific recommendations for physical activity for men and women of different ages and risks need to be established experimentally. For whom is it safe to exercise, at what level, and for how long? Research of this nature, enhancing understanding of the role of physical activity in cardiovascular health, would permit clearer public health recommendations.

IV. Personal Attributes

A. Serum Lipids-Lipoproteins

The relationship between high density lipoprotein (HDL) and risk should be evaluated by considering both the interaction with other risk factors and the known determinants of HDL. The current clinical trials in MRFIT, and the followup of the LRC prevalence studies, the Framingham cohort, and some of the studies of the SCOR-A program should become sources for further studies of HDL and disease. Studies should be expanded to encompass work on the various apoproteins and to involve other racial and ethnic groups, such as blacks and Mexican-Americans. The endpoints for these studies should include coronary heart disease, stroke, and peripheral vascular disease.

B. Blood Pressure

The relationship in older age groups between blood pressure (especially "pure" systolic hypertension) and disease (including coronary

heart disease, stroke, and senile dementia) should be evaluated. Similarly, the effectiveness of blood pressure reduction in older age groups--including treatment of "pure" systolic hypertension--needs to be evaluated by controlled clinical trials.

Epidemiological studies are needed of the biochemical interrelationship with blood pressure (renin, dopamine, kallikrein) and risk of disease.

The major goal of further blood pressure research should, however, be oriented toward primary prevention of hypertension, including evaluation of nutrition, eating, and exercise patterns both in children and adults, along with genetic and other environmental and social factors.

V. Thrombosis

The complex process of clotting appears to be involved with the atherosclerotic process and with clinical coronary heart disease at three levels. The thrombotic process appears to be intimately involved in the middle and later stages of atherogenesis during which many plaques apparently grow by organizing and incorporating thrombi into their substance. Autopsy studies have shown that recent thrombosis forming on atherogenetic plaques may be involved in many, if not most, myocardial infarctions. Recent animal studies indicate that blood and blood platelets contain growth factors capable of stimulating vascular smooth muscle cells to proliferate. Since such cell growth is an intrinsic part of plaque development, it is now theorized that the initiation of atherogenesis arises with the loss of normal endothelial barrier function and the exposure of the intima to whole plasma or to platelets as well.

During the last decade there has been an elaboration and refinement of tests for coagulation, platelet behavior, and thrombosis. However, these tests are largely confined to expert laboratories, and few of them are easily taken into the field for epidemiologic or cohort studies. But they are applicable to case-control studies and limited population studies of the prospective type. It is a common opinion among experts that, except for a few special disorders such as von Willebrand's disease, the currently limited knowledge of the details of the relation of thrombosis to atherosclerosis does not permit the selection of a few special laboratory tests that can be assured to measure relevant and discriminating aspects of thrombotic tendency. This area may benefit considerably from investigation of multiple aspects of clotting in case-control studies.

Meaningful data have accumulated on the relation of the use of oral contraceptives by women to incidence of venous thromboembolism and liability to heart attack and stroke. Similar effects on heart attack among men were experienced in studies of estrogens in the treatment of prostate cancer and as a lipid-lowering agent in men recovered from heart attacks. Further research into the role of these substances as thrombotic agents is needed.

Recommendations

1. The lack of a clear understanding of the role of salt consumption in determining blood pressure levels has handicapped the development of programs for the primary prevention of hypertension. Data are needed to guide nutritional advice for infants, children, and adults. Because observational studies have failed to resolve the issues, it is recommended that clinical trials be undertaken to assess the effects of reduced salt intake on blood pressure levels in infants, children, and adults. These trials should encompass samples of persons with normal blood pressure levels as well as those who are already hypertensive or hypertension-prone (i.e., borderline hypertension, family history of hypertension, or labile hypertension). The studies of salt intake should be linked with studies of weight reduction, so that confounding of these two interrelated variables can be taken into account.

2. Every effort should be made to encourage current cigarette smokers to quit. Meanwhile, health education programs should be carried out and evaluated to influence the rate of people--especially youngsters--starting to smoke. Surveillance of smoking behavior nationally, regionally, and among different socioeconomic-educational-ethnic strata should be continued and expanded, and should include objective measurements of smoking and dose.

3. Methods should be developed for the improved description and measurement of physical activity and fitness in the general American population and specific subgroups. Such measures should be used to study the type, duration, frequency, and intensity of physical activity required to enhance prevention of the emergence of cardiovascular risk factors (e.g., hyperlipidemia, obesity, hypertension, and diabetes) and cardiovascular diseases. Possible hazards and risks of physical activity should also be assessed.

4. Major changes in important risk factors occur between adolescence and middle age, at the time of changes in lifestyle. If excessive increase in risk factors could be prevented, then later disease might be avoided or postponed. Therefore, careful longitudinal studies should be developed to determine which environmental and genetic factors lead to an increase in the risk factors during this age span.

   Such studies should examine:

   a. The relationship of lifestyle changes, including diet and physical activity, to changes in the standard risk factors.

   b. The relationship of hormonal and other biologic changes occurring during puberty to risk factor changes in both sexes.

   c. The relationship of hormonal changes due to menstruation, oral contraceptive use, pregnancy, and menopause to risk factor changes in women.

5. Studies are needed on the distribution and health effects of risk factors in special population groups. Specifically, the distribution and trends of risk factors should be measured in the black, Mexican-American, and Native American populations, including groups undergoing acculturation, as well as the relationship of risk factors to cardiovascular diseases in these populations. The special features and determinants of risk factor distributions in these populations should be investigated. Possible examples include:

    a. Hypertension, hyperglycemia, and obesity among black women.

    b. Relatively higher HDL cholesterol among blacks.

    c. Hypertriglyceridemia, obesity, and diabetes among Mexican-Americans.

    d. Diabetes among Native Americans.

6. Levels of plasma lipoprotein fractions may be set early in life by diet and eating patterns and perhaps by other family influences. In turn, these factors may affect the level of risk factors and the development of cardiovascular disease in adults. Longitudinal studies, starting at birth and lasting through childhood are needed (at least to 5 years) to examine plasma lipid patterns and their evolution in infants and their families. Particular attention should be paid to genetic and environmental factors possibly influencing levels, variability, and trends in plasma cholesterol and its lipoprotein fractions.

7. Sizable differences in coronary and stroke death rates exist among geographic areas of the United States. The reasons for these differences are not fully explained by variations in known risk factors. The following are therefore recommended:

    a. Surveillance of incidence and mortality in geographic areas with high, intermediate, and low death rates.

    b. Measurement of risk factors and social and environmental variables in these areas.

    c. Surveys of genetic factors.

8. Risk factor measurements usually have been obtained at rest in the environment of the medical clinic. It may be important to determine the dynamic short-term changes in risk factors and behavior which occur during the challenges of daily life. Variability in risk factors may be an important predictor and determinant of disease. Therefore, studies of the dynamic changes over time of blood pressure, cholesterol, weight, activity, and smoking should be considered. These studies should take into account the relationship of risk factor variability to:

    a. The behavioral characteristics of the individual (for example, Type A-B behavior pattern).

b. The environmental situation, such as type of work, psychosocial dynamics of the work situation of individuals and groups, activity, etc.

c. Neurohumoral and endocrine profiles of the individual.

d. Subsequent risk of disease.

Psychosocial and Physical Environment

The importance of environmental factors in the etiology of coronary heart disease is emphasized by the dramatic differences in CHD rates among and within countries of the world and by the fact that migrants tend to assume the rates of the areas to which they move. The differences in rates observed among these groups are large and persistent, and strongly implicate environmental factors in CHD etiology.

Environmental factors encompass a broad range of physical, chemical, social, and psychological factors that interrelate with one another in complex ways. Research into the psychological effects of the environment on CHD has been underway for over 20 years, and a series of promising findings have emerged that now present an excellent opportunity for further study. On the other hand, research into the effects of the physical environment on disease is in a very early stage, and therefore a more exploratory research strategy is indicated. Consequently, the following two sections consider research priorities separately for psychosocial and physical factors. These two sections outline separate programs of research needed to better understand the way in which these environmental factors affect the occurrence of the disease.

Part I: Psychosocial Environment

A variety of psychosocial factors has been studied in relation to the etiology of CHD. From this research, two related factors--Type A behavior pattern and cultural mobility--have emerged that are supported by relatively strong and consistent empirical evidence. (Other psychosocial factors have been investigated, but their association with CHD is not yet as clearly documented.) Continuing research on these factors is nevertheless warranted to better establish their significance. The following sections outline a program of needed research.

I. Type A Behavior Pattern

One of the most promising and actively researched psychosocial risk factors for coronary heart disease is the Type A behavior pattern. Several studies, including the Western Collaborative Group Study and the Framingham Heart Study, have found a strong association between the TABP and the incidence and prevalence of coronary heart disease. Further research is now needed to clarify this important relationship. Specifically, carefully designed studies should be initiated to:

- Determine the distribution and predictive power of TABP for CHD in general and selected populations.
- Determine the origins of TABP.

- Determine the biological and physiological pathways through which the TABP operates to influence coronary atherosclerosis, its complications, and the incidence of CHD.

- More precisely define the TABP for use in clinical and research settings.

- Determine the prospects for CHD prevention through modification of adverse TABP parameters.

A. Distribution and Predictive Power of TABP in Other Cultures

Very little descriptive information is available on the distribution of the Type A behavior pattern by age, race, sex, socioeconomic status, specific occupations, and different cultures or over time. In addition, the relationship of occupational and geographic mobility, urbanization, and status incongruity with the prevalence of the TABP is virtually unknown. Since most of the research on TABP has been conducted among white U.S. males, future investigation should examine the association of TABP with CHD in selected and general populations of different sex, color, socioeconomic status, and culture. Studies in countries with coronary rates significantly higher or lower than in the United States are indicated, since these studies might be very helpful in explaining the notable differences in CHD rates among U.S. populations as well as among different countries. Likewise, the effect of TABP on CHD in populations experiencing mobility and change should be examined. There is limited evidence suggesting that at least one of these factors--occupational mobility--may interact with Type A behavior in markedly affecting CHD rates.

B. Origins

The origin of TABP remains inadequately researched. It is not known whether TABP has a significant genetic component or whether it mainly evolves from learned behaviors and other parental or external influences in early childhood, adolescence, or adulthood. Since the two prospective studies relating TABP to CHD have found associations primarily among men employed in white-collar occupations, one might postulate that certain environmental challenges may precipitate this behavior. Also, certain cultures may reward or penalize their members for this behavior. As a minimum, research is needed to separate Type A behavior and its subgroups according into at least three components:

- Personality predisposition.

- Learned behavior.

- Demands of the particular cultural or work setting.

C. Biological and Physiological Pathways

Several major epidemiologic studies have found that the TABP operates independently of the standard risk factors in its association with prevalence and incidence of CHD. Since TABP is unrelated to cigarette smoking and to casual levels of blood pressure and cholesterol, other physiological

factors must be examined. Specifically, Type A's should be compared with Type B's to determine differences in various clotting factors, neuroendocrine parameters, and other biochemical and physiological factors. The study designs should allow for comparisons using both resting values and dynamic responses to challenging psychological and physiological tests as well as in varying occupational stress situations. In this light, the measurement of blood pressure, heart rate, cholesterol, and smoking lability during daily conditions may be a profitable area of investigation. It is of great importance to study the pathways for both underlying coronary atherosclerosis and incidence of CHD.

D. Assessment

At the present time, several methods are available for assessing the Type A behavior pattern. The two most commonly used are the Structured Interview, developed by Dr. Ray Rosenman and Dr. Meyer Friedman, and the Jenkins Activity Survey (JAS), a self-administered, computer-scored questionnaire. Each measure encompasses a particular complex of responses to assess levels of aggressiveness, competitiveness, job involvement, impatience, need for achievement, and actual or potential hostility. Further work is needed to delineate specific aspects of TABP related to subsequent development of CHD. These factors should then be rigorously defined so that their impact on CHD in varied populations and study settings can be evaluated by clinicians as well as epidemiologists.

E. Prevention

One of the most striking gaps in our knowledge about the Type A behavior pattern is the lack of data on either behavior modification of the TABP or possible pharmacologic intervention on the TABP in the prevention of CHD. Methods for modifying key aspects of TABP must be developed, especially in the context of the modern occupational career and setting. The use of various potential TABP modification support systems, including family, supervisors, and community, should be explored. Likewise, the role of exercise in influencing TABP and reducing coronary risk among Type A's might also be explored. The effect of behavior modification on various biologic parameters should be incorporated into these studies.

If behavior modification is found to be infeasible or undesirable, then pharmacologic approaches to modifying the biologic vulnerability of Type A's should be evaluated.

II. Mobility, Migration, and Social Change

It is important to initiate a systematic program of research to clarify the relationships of various forms of mobility, migration, and social change to CHD. Higher rates of CHD have been observed among persons experiencing many different types of changes. These include changes in job, residence, and country as well as changes among those upwardly mobile in relation to their parents and among those who remain stable themselves but whose world changes around them. The common denominator in all of these cases is change. The major research in this area should assess:

- The importance of selection factors. Migrants probably represent a selected group; their subsequent disease experience may be a reflection of these selective factors instead of environmental influences. Studies of the disease experience of migrant populations should include standardized comparisons of the disease experience of those who remained in the home country. In addition, where possible, migrants should be studied in two or more new places to assess the importance of selective factors.

- The importance of the new environment. Migrants often experience changes in diet, occupation, physical activity, climate, water quality, and other factors. The subsequent disease experiences of migrants may be due to the effects of these factors rather than to changes per se. Studies of migrants should include the assessment of acculturation patterns so that disease rates can be compared among those who have retained their old ways versus those who have adopted new lifestyles.

- The importance of mechanisms linking social change to CHD. This clearly is an area requiring considerable research. One aspect that must be clarified is the psychosocial significance of change. For example, it is possible that various types of social change affect interpersonal relationships. This is evident in the case of the loss of spouse through death or divorce; it is probably also true in instances of job or residential change. To assess all of these relationships, it is important to study the role of social support networks in modifying the effect of life changes. In particular, the role of family, friends, and associates should be assessed in relation to such changes. It is important to develop such specifications so that studies can be initiated relating biological mechanisms to disease outcomes.

To implement research on these issues, three major strategies can be suggested. One would be to conduct research in population groups that typically experience little change. Studies of religious sects and residents of remote rural places offer important research opportunities. Unfortunately, members of these special groups often differ from other people in so many other ways (including genetic) that it is difficult to assess the relative importance of each of the various factors. One approach to this problem would be to study members of these groups in different countries and places. For example, Seventh-Day Adventists, Mormons and others might be studied in differing environmental settings. Another approach would be to study these groups as they change. For example, the Japanese in Japan have for centuries emphasized the importance of stable residential patterns while holding one lifetime job and having one lifetime set of friends. This is now changing, with employees either moving to new companies or being transferred to new cities. Again, the role of other factors (diet, occupation, smoking, physical activity, etc.) must be evaluated in such research.

A second strategy would be to study migrant populations more intensively. Such research should attempt to study migrants in two or more different

environments, to study both migrants and their second-generation and third-generation offspring, and to compare migrants who have acculturated to their new environments with those who have retained their traditional culture. In these studies, it is essential that attention be given to concomitant changes in such other factors as diet, smoking, physical activity, occupation, and living circumstances.

A third strategy would be to study population groups that are undergoing rapid social change, both in this country and throughout the world. For the most part, these changes involve increasing industrialization, urbanization, and population density. Studying the original residents who experience these changes would be valuable, since these residents remain stable while the world about them changes. Results from studies of this type, however, are difficult to interpret since so many factors typically change at the same time. One approach to this problem is to undertake studies of such groups in many different places in an effort to discern common factors.

These proposed studies should attempt to determine causal relationships with basic coronary atherosclerosis as well as with the incidence of clinical disease.

Little population-based research has been conducted on the biologic factors associated with migration, mobility, and social change. A few studies have found increases in serum cholesterol and blood pressure levels among those experiencing social change. However, these limited observations do not permit a thorough assessment of the relationship between social change and CHD. A much more systematic and intensive program of research focusing on a broader range of physiologic and biochemical mechanisms is needed to clarify the links betwen social change and CHD.

III. Determination of Common Denominators

An important goal of research on Type A behavior pattern and migration, mobility, and social change is to determine their possible common denominators. There are two aspects to this problem:

a. The study of those psychological and social processes that accompany both TABP and mobility.

b. The common physiological pathways whereby TABP, mobility, and other psychological parameters may be causally related to the accelerated development of coronary atherosclerosis and the incidence of clinical disease.

IV. Other Psychosocial Factors

Although Type A behavior and mobility appear to be the most productive areas for future research on psychological factors and CHD, other areas should be mentioned. These include more comprehensive research into the relationship of occupation or work setting and other psychological states (e.g., tension or suppressed hostility) to the incidence of CHD.

A. Occupation

Over the past 50 years, numerous investigators have examined the effect of occupational status and occupational stress on coronary heart disease. The conclusions that can be drawn from these studies are ambiguous and unclear, but it appears that occupational level, whether high or low, has not been consistently associated with CHD. Few researchers, however, have focused on the work environment per se as it affects individuals. For example, occupational mobility in the form of job changes, promotions, or demotions has been examined in very few studies, with equivocal results. These studies generally have not examined the meaning of job promotions or demotions for the individual and whether this change is consistent with personality, goals, expectations, or capabilities. We do not know the effect on CHD risk of intracompany transfers to other geographic locations or of such job factors as boredom, helplessness, insecurity, alienation, and unemployment.

Similarly, the short-term physiologic effects of work overload or underload, deadline pressures, or holding multiple jobs have not been examined across a variety of occupations. In addition, interpersonal support systems on the job, such as support from supervisors or fellow workers, have not been examined as a protective mechanism against CHD.

Since a majority of persons spend a considerable amount of time on the job, the possible disease effects of these issues deserve exploration.

B. Other Psychological Factors

Despite major campaigns to inform the public of the primary causes of coronary heart disease, recent public opinion polls have found "emotional pressure, worry, and anxiety" named more frequently as the likely cause of CHD than cigarette smoking, high blood pressure, or cholesterol level. At least three prospective studies have shown measures of anxiety or tension to be associated with the incidence of CHD. In addition, it appears that suppressed hostility, measured by a variety of techniques, may be an independent predictor of CHD. Systematic study of these psychological factors is difficult, however, primarily because there are few reliable and valid methods for their assessment. This area is of potential importance, and methodologic research dealing with these other psychological factors should be encouraged.

V. Specific Populations to be Studied

A variety of specific population groups can be identified as providing excellent settings for research on psychosocial factors in CHD:

- Migrants within the United States who move from low-rate to high-rate areas (e.g., residents of Appalachia who move to urban areas; southerners, both black and white, who move north; and residents of small towns moving to large urban areas).

- Members of low-risk groups such as Seventh-Day Adventists and Mormons (lifelong members and converts), vegetarians, first-generation and second-generation Japanese and Chinese, and Chicanos.

- Migrants from low-rate countries to countries with higher rates. Work has been done on residents of such low-rate countries as Japan, Puerto Rico, and Yugoslavia and on migrants from at least one of these countries (Japan), but psychosocial factors have been covered only in a very preliminary way. Further and more intensive study of such groups is clearly warranted.

- Residents of areas undergoing rapid social change, industrialization, and urbanization (including rural areas in the United States, Eastern European towns, Japan, and areas in the South Pacific).

- In the past, women have received little attention in epidemiologic studies, in part because their CHD rates have been consistently lower than those of men. Can this lower rate be explained, at least in part, by a possibly lower prevalence of TABP in women or a lesser mobility of women than men in our society? Comparison of coronary rates among working women and housewives should help in answering such questions. Similarly, studying coronary rates among working women according to occupation and job responsibility, marital status, number of children, TABP, and mobility may provide useful clues to the importance of the workplace in explaining sex differences in CHD.

- Very little research has been conducted on psychosocial risk factors in children. The origin of Type A behavior might be found by examining school grades and achievement among children, child-rearing and child-parent relationships, and measures of aggressiveness in the early school and home settings.

VI. Methodologic Considerations

Research in the area of psychosocial factors is difficult, and rigorous methods are essential. Better techniques for assessment and measurement must have first priority in this research field. Especially important is the more rigorous definition of stress and distress and measurements of their effects upon humans.

The following are some additionally important considerations:

- Longitudinal studies should be undertaken involving psychosocial and occupational parameters, especially in relation to CHD, CHD risk factors, and such other diseases as cancer and stroke.

- Dynamic monitoring of risk factors should be initiated in studies, including the effects of static and changing psychosocial and occupational conditions on the level of the usual risk factors as well as on new parameters (including neurohormonal biochemistry).

- The effects of psychosocial indices and changes should be studied in relationship to the precipitation of clinical coronary events, including sudden coronary death. The roles of fatigue, overload, recent life events, deprivation and loss, sleep deprivation, and exhaustion, anxiety, and denial should be studied in the same context.

- The incidence and type of recurring CHD events should be studied in relationship to psychosocial indices, psychological factors, and behavior pattern type.

- The effects of TABP and other psychosocial parameters should be studied with regard to compliance, utilization of medical services, self-report of illness, and alterations in other CHD risk factors, such as blood pressure, serum cholesterol, and cigarette smoking.

- The relationship between a change in psychosocial factors and the decline in mortality from coronary heart disease should be investigated.

Part II: Physical Environment

In addition to the social and cultural milieu, various physical and chemical agents in the environment are known to play a role in the production of human disease. The arguments for an important role of such environmental factors in the etiology of coronary heart disease are those outlined above--large, persistent differences in CHD rates in different places, the fact that migrants tend to assume the rates of the area to which they move, and the association of high rate areas with industrialization and environmental pollution. The fact that age-specific coronary heart disease incidence and mortality rates are so much lower in some parts of the world than in the United States--in Japan and in parts of southern Europe, they are approximately 25 percent of U.S. rates and probably lower in developing countries--and the fact that U.S. rates may have risen dramatically from the preindustrial period to the present, suggest that the contemporary U.S. environment may be more important in the etiology of CHD than has been shown by available research results.

It is difficult to confirm the impression gained from cross-cultural studies that environmental factors may be important in the etiology of CHD, because there are too many possible explanations for the difference between cultures in CHD rates. Between the U.S. and low-rate areas there are substantial differences in exposure to innumerable physical agents and chemicals, in food, air, water, and the workplace environment. Compounding the difficulty is the fact that there are many differences unrelated to the physical or chemical environment as well.

On the other hand, the lack of evidence on environmental factors available from controlled studies within homogeneous populations is not a strong indication that these factors are unimportant. It may be due largely to the lack of variation in exposure to physical and chemical factors among members of the populations studied. Studies within the United States, for example, may not provide measures of any effects on cardiovascular health of the changes in food composition resulting from food processing practices,

because of the ubiquity of processed foods in American diets. Nor can such studies be expected to provide an explanation for the fact that nearly all Americans have high serum cholesterol levels compared with those of citizens of low-rate countries.

In summary, comparison between cultures suggests that the environment to which most Americans are exposed might be important in the etiology of CHD. Little solid evidence of this is available, however, because (1) in comparisons between cultures many differences are identified, any of which might be explanatory, and (2) in studies of homogeneous populations the lack of variation in relevant exposures may prevent the discovery of their importance. For these reasons, progress has not been easy in this area, and in the future it will depend on the use of innovative study approaches.

Chemicals that ultimately become widespread in the environment often are manufactured, processed, or handled in a way that leads to the exposure of a group of workers. Such workers often experience much higher doses than does the population at large, and thus can be studied advantageously for possible effects. Many such studies have been done on occupational carcinogenesis; almost none have been done on occupational atherogenesis. This is due, in part, to a number of difficulties shared by both kinds of inquiry--long latency period from onset of exposure to onset of disease, complex multifactor exposure history of many workers, unavailability of records, and mobility of workers. In addition, there are the usual problems of assessment of the endpoint, CHD. Studies in this area are thus vital, yet remain inadequate.

Besides exposure in the workplace, human beings are exposed to chemical agents through food, water, and air. Such population-based exposures may be important because even minute increases in risk, when spread across a whole population, could contribute substantial amounts of morbidity or mortality. No such exposures are well-characterized, but studies of rates of heart disease and water hardness are suggestive, and further investigation based on specific hypotheses is needed.

Cigarette smoking is an example of an important factor in the environment of the individual. Another example involves personal dietary preferences. Study strategies appropriate to exposures which are under individual control are different from those considered in this section, and individual factors such as these are considered elsewhere in this report.

I. Occupational Studies

Very little is known about the distribution of causes of death or morbidity across occupations with potentially toxic exposures. A number of plausible biologic mechanisms suggest that data on occupational exposures and CHD mortality would be rewarding in developing etiologic hypotheses. Specific probable mechanisms for atherogenesis, CHD, or CHD-related sudden follow:

- Anesthetic gases, such as cyclopropane and halothane, potentiate the arrhythmogenic effect of endogenous catecholamines. A number of chemicals that are present in the workplace or the environment

have structural similarities that suggest they may have similar effects on the myocardium; these chemicals have extremely long tissue half-lives and thus could represent a long-term hazard. Examples of such chemicals include the polyhalogenated hydrocarbon pesticides (DDT, DDE, dieldrin, etc.) and industrial chemicals (PCF's and PBB's). Studies of sudden death should exploit this similarity and include inquiry into occupational exposure to such chemicals as well as chemical analysis of appropriate tissues for chemical residue levels.

- The polyhalogenated hydrocarbons bind to estrogen receptors and are estrogenic in animal systems. Persons occupationally exposed to pesticides have been noted to have elevated HDL cholesterol and triglycerides. This finding is consistent with an estrogenic chemical effect, and these observations demand further investigation to determine whether such exposure changes CHD mortality risk, CHD incidence, or the occurrence of CHD-related death.

- The neoplastic theory of atherogenesis, while not firmly established, is extremely far-reaching in its implications. If exposure to mutagenic substances plays a role in atherogenesis, then the same worker populations now being investigated for increased risk should be followed for increased rates of atherosclerotic diseases and CHD.

- Various chemical and physical stresses could easily lead to hypertension and its attendant complications. A number of mechanisms exist for occupational chemical and physical exposure to produce the entire spectrum of atherosclerotic disease, including CHD and CHD-related sudden death. However, little work has been done on the distribution of causes of death, including CHD death, by occupation. Initially, mortality studies of CHD by industry should be done. Workers being followed for occupational cancer should be followed as well for CHD mortality. Inquiry into work-related CHD mortality would be made much easier by the coding of occupation on death certificates.

II. Water Constituents

Although the literature is not consistent, a number of studies have shown associations between soft water and CHD mortality. The relationship is not strong, but this is to be expected, since the water a person drinks usually does not contain a large proportion of his daily intake of biologically important elements. Certain findings in this area, however, suggest areas where more specific research might be fruitful. The increased rate of sudden coronary death found in several soft water areas provides a hypothesis regarding the role of magnesium which is plausible considering that soft water has low magnesium levels, processed foods typical of western diets provide magnesium intakes which some authors consider marginal, and magnesium has an important role in the regulation of heart rhythm. Other studies show increased absorption of the toxic element lead among residents of soft water areas. The role of magnesium and lead and other

elements such as cadmium, copper, and zinc should be studied in individual patients. Cities where water supplies are modified offer particularly appropriate opportunities to study the effects of water minerals.

III. Methodological Considerations

- The Task Force on Environmental Cancer, Heart, and Lung Disease presented its first annual report to Congress in August 1978. During the following year the task force will be considering methodologies suitable to environmental monitoring and the assessment of pollutant burden in biological samples. NHLBI is a participant in the task force and will be in a position to benefit from developments in these areas which open new areas for study of possible cardiovascular effects.

- Sudden, arrhythmic death represents an important avenue for the study of environmentally related CHD mortality, both for occupational exposures (as noted above) and for population exposures. Since most sudden death is referred for coroner investigation, protocols should be established both for obtaining occupational history from relatives of sudden death victims and for chemical analytic inquiry into the body burden of chemical pollutants borne by decedents.

Recommendations

Based on the previous documentation, the following areas have high priorities for future research on the etiology of coronary heart disease:

1. Several studies have observed a strong association between Type A behavior pattern and coronary heart disease. Further study of this behavior pattern is needed, with special emphasis on its predictive power in various selected population groups, its determinants, and the biologic mechanisms linking TABP to coronary atherosclerosis and its manifestations.

2. Higher rates of coronary heart disease have been observed among persons experiencing various types of life change and mobility. Further study is needed of persons who experience social change, migration, and mobility, with particular emphasis on geographic and cultural groups known to exhibit different rates of CHD. Special focus should be given to the psychosocial and biologic mechanisms linking social change to CHD.

3. To assess whether specific physical and chemical exposures are important contributors to the high incidence of CHD (including sudden death) in industrialized nations, investigation is needed into the possible cardiovascular effects among persons with the relatively high exposures occurring in various workplaces. Studies are recommended among specific occupational groups to assess the role of chemical and physical exposures in the etiology of coronary heart disease and sudden death in possible high-risk industries. Systematic work is needed on the relationship of occupation to CHD mortality in the United States over time.

4. Differences in CHD mortality rates between geographic areas differing in the hardness of local water supplies remain to be elucidated. Further studies are needed relating CHD and risk factor levels to exposure of individuals to components of drinking water such as magnesium, lead, cadmium, copper, and zinc.

Epidemiology and Heart Disease in the Young

The Task Force on Prevention and Treatment of Cardiovascular Disease in the Young has addressed a broad range of research issues that relate to heart and vascular diseases affecting infants, children, and adolescents. The report of the task force provides a thorough review of all aspects of heart disease in the young. This chapter summarizes the recommendations as they relate to the epidemiologic study of heart disease in infants and children.

We now have compelling evidence that the disorders of arteriosclerosis and hypertension have their origins during childhood. These two diseases, which are the most common causes of adult death in the United States, progress slowly, and it is not until adult life that serious manifestations of coronary heart disease, heart failure, stroke, and renal disease occur. The majority of this report discusses the present epidemiologic challenges that relate to arteriosclerosis and hypertension, not only in adults but also in infants and children. This chapter therefore deals only with unanswered epidemiologic questions that relate to congenital heart disease, cardiovascular disorders related to premature birth, rheumatic heart disease, and cardiomyopathies, which are the major cardiovascular disorders affecting infants and children. Although these disorders are numerically less frequent than arteriosclerosis and hypertension in the adult population, they cause a significant burden of suffering in infants and children and a disruption of family life. These illnesses take a toll in extended cost to society, often lasting from infancy through adult life.

I. Congenital Heart Disease

Congenital heart disease (a structural abnormality of the heart or the intrathoracic great vessels) affects 8 to 10 of every 1,000 infants born alive. About 1 newborn per 1,000 live births has a heart defect that cannot be helped by medical or surgical management. Some 5 to 6 per 1,000 live births need frequent medical and surgical attention. Because of successful new therapy, infants who previously would have died now survive into adulthood. There is increasing evidence that a minor congenital deformity of the aortic valve (bicuspid aortic valve) undergoes a slow degeneration and narrowing, resulting in significant symptoms that require medical and surgical care during adult life.

The incidence of most congenital heart disease has remained stable, but there are unexplained increases in reported ventricular septal defects and patent ductus arteriosus. On the other hand, preventive strides have been made in the last decade. An effective rubella vaccine has reduced the number of infants born with rubella-caused congenital heart disease. The incidence of congenital heart disease resulting from Down syndrome has also decreased, because older women are having a smaller proportion of all babies. Further reduction in this type of CHD should occur because

of prenatal chromosomal diagnoses for older women. We have learned that alcohol, anticonvulsants (trimethadione), and drugs used to treat mental illness (lithium) can cause congenital heart disease. We have also learned that some congenital heart diseases have a pure (single gene) genetic origin. In spite of this progress, however, we do not know the cause of most heart disease in the young nor do we have adequate prevention strategies.

At conception, an embryo receives a genetic makeup that will set limits on its ultimate development. In some situations, the embryo will receive a single gene that will in most bearers cause congenital heart disease, such as Holt-Oram syndrome. At present, there are no known environmental manipulations to overcome the presence of this single gene disorder.

The majority of embryos have a genetic potential for normal cardiovascular development that can be overridden by environmental influences. In some situations, the obnoxious environmental influences are so powerful that normal cardiovascular development is interrupted in a high percentage of embryos (rubella). In other embryos, their unique genetic background may make them susceptible to an environmental agent that almost all other embryos resist. There are those who believe that the majority of congenital heart disease arises from such subtle, multiple, genetic-environmental interactions.

Epidemiologic studies focused on the genetic potentials and the prenatal and postnatal environment are needed to elucidate etiology and to devise prevention strategies for congenital heart disease. For example, the study of the gestational histories of mothers who had babies with similar defects of the heart may provide important leads for the prevention of malformations in other pregnancies. Regional, racial and time analyses may provide the leads to the discovery of new causes of congenital heart disease. In addition, the most cost-effective means of providing quality medical care for those affected by these disorders of the circulation should be studied epidemiologically. Such studies should seek to obtain the most effective method for managing infants and children who have congenital cardiac malformations. Short-term and long-term outcomes of specific types of surgery for particular lesions could be assessed. Factors important in the rehabilitation of patients with congenital heart disease, including psychosocial factors, could be elucidated. To make health planning more effective, the benefits and costs could then be determined from the long-term outcomes.

Most young infants or children with congenital heart disease are cared for in regional diagnostic and treatment centers. This grouping for care provides a unique opportunity to explore the causes of congenital heart disease and evaluate the effectiveness of medical and surgical therapy. Advantage should be taken of the nationwide network of organized clinical centers for congenital heart disease. Regional centers such as the New England Regional Infant Cardiac Program and the Crippled Children-designated centers should be utilized and expanded based on need. NHLBI should organize a unified form of data collection and assure that the data collection and its epidemiologic analyses reach their full potential, which will facilitate discovering not only the best means of therapy but also the causes of congenital heart disease.

To accomplish this goal, NIH (NHLBI) should organize a workshop to discuss the method of establishing a unified reporting system for congenital heart disease along with other birth defects and other cardiac disorders, such as cardiomyopathy. The feasibility of such a system should be evaluated in terms of cost and benefit. It should also examine the desirability of a prospective study of pregnant women to seek and evaluate potential cardiac teratogens. The capability of existing data collection systems at CDC, CC, or NCHS and their expansion should be considered.

International surveys should also be conducted on patients with congenital heart disease who are operated on late or not at all because cardiac surgery is unavailable. These data would be helpful in assessing the natural history of various forms of congenital heart disease.

Because of a need for more accurate data on death certificates about congenital heart disease in abortuses and stillbirths, where the incidence is thought to be very high, a standardized autopsy guideline should be created to provide a clearer picture of the incidence of congenital heart disease among abortuses, stillborns, and infants. NHLBI should sponsor a workshop of interested pathologists, pediatric cardiologists, epidemiologists, and staff members from NCHS, CC, and CDC to discuss this problem.

A study should be conducted to investigate whether the children of congenital heart disease patients have an increased incidence of cardiac malformations. The study should be implemented by NHLBI in representative centers across the country.

Standard noninvasive techniques should be developed to allow the accurate diagnosis of aortic valve abnormalities and to study the evolution of valvular degeneration. Congenital bicuspid aortic valves form the nucleus for the development of calcific aortic stenosis, which often results in severe heart disease in adulthood and requires heart surgery. The incidence of this congenital lesion and the factors resulting in valvular degeneration are currently unknown.

II. Cardiovascular Disorders Related to Prematurity

According to current estimates, 72 newborns per 1,000 live births in the United States weigh less than 2,500 gm. It is estimated that 40 to 50 percent of all infants with birth weights under 1,750 gm will maintain a patency of their ductus arteriosus. In some, this will result in severe congestive heart failure and, if not appropriately managed, prolonged hospitalization and death. Prevention of prematurity would lower this common cardiovascular cause of infant morbidity and mortality. Various therapeutic methods need evaluation in the absence of prevention.

There is experimental evidence indicating that (1) prostaglandins cause the ductus to remain patent during gestation; (2) the immature ductus arteriosus responds less well to the oxygen stimulus; (3) the immature ductus arteriosus constricts with the administration of indomethacin, a prostaglandin inhibitor; and (4) the immature lung does not metabolize prostaglandins as well as does the mature lung. Many institutions are now using indomethacin therapy to treat premature infants who have

problems associated with patent ductus arteriosus. The efficacy of this therapy and its long-term effects, however, are not known.

A prospective study of the incidence and management of patent ductus arteriosus in preterm infants should be performed under the auspices of NHLBI. From this study, a clearer picture of the magnitude of the problem of special health care delivery can be defined. In addition, clinical trials of the use of prostaglandin inhibitors that cause the ductus arteriosus to close should be undertaken together with a long-term study of different management schemes. The long-term effects of indomethacin must be studied before general acceptance of this form of therapy can be recommended for all newborn infants with patent ductus arteriosus.

III. Cardiomyopathies

Throughout infancy and childhood and into adult life, disorders of the heart muscle known as cardiomyopathies may occur. These result from infection with viruses and other agents, alcohol, heritable disorders, and factors yet to be elucidated. When cardiomyopathies occur, heart failure may follow, with severe disability and often early death. In other cases, a chronic limiting disorder results. The disorder of mitral valve prolapse has become increasingly recognized as causing recurrent cardiac symptoms, such as chest pain and rhythm disturbances. In some instances, sudden death occurs. One theory of the cause of this disorder postulates a disturbance of the papillary muscles of the left ventricle.

The prevalence of disorders affecting the cardiac muscle is not known. To have a clear picture of the magnitude of this health problem, a registry of cardiomyopathies would prove extremely valuable. In view of the potential value of setting up such a registry as well as its potential cost, the value of such existing data collection agencies as the National Center for Health Statistics should be examined to determine whether their operations can be adapted for this purpose.

IV. Rheumatic Fever

The etiology of rheumatic fever and rheumatic heart disease is known, and highly effective, but not perfect, preventive biologic technology has been available for several decades. Nevertheless, the diseases have not been eradicated in the United States. A dramatic lowering of the incidence of acute rheumatic fever has occurred in this country since the 1930's, but the incidence in the 1960's in several American cities is still 25 to 50 per 100,000 children 5 to 14 years of age. In addition, these diseases are increasingly understood to be a substantial public health problem of children in developing countries. If substantial additional progress toward eradication is to occur, certain epidemiologic studies and activities are needed and should be encouraged and supported.

NHLBI, in collaboration with the Center for Disease Control, Crippled Children's Program, state health departments, and local volunteer organizations, should encourage the study of the various current prevention strategies for rheumatic fever and rheumatic heart disease to determine

the most effective way to eradicate them. NHLBI should sponsor a workshop or series of workshops to consider what kinds of studies should be performed to learn how long and what kind of primary and secondary prevention should be practiced.

There is a need to better define the incidence and prevalence of rheumatic fever, rheumatic heart disease, and bacterial endocarditis and to define those at risk. Such studies are the only way we can know in a timely fashion what progress has been made. Population-based studies are needed, with careful analyses of data by subpopulation classification, such as race and socioeconomic standards.

Consequently, NHLBI, in conjunction with the National Cancer Institute's SEER(s) program, should explore the possibility of adding the diagnoses of rheumatic fever, rheumatic heart disease, and bacterial endocarditis to its purview, because this promises to be a most cost-effective method. National trends should be followed up by one of the NCHS's recurring Health Interview Surveys. These monitoring programs should also be used to determine the role of viral myocarditis in valvular disease and the incidence and natural history of the newly described mitral valve prolapse syndrome.

Rheumatic fever and rheumatic heart disease are international health problems. In some Third World countries, the incidence is very high. It is only in these countries that certain studies concerning the related epidemiology and care of victims can be done. Consequently, these studies should be supported.

Bacterial endocarditis still occurs among those with valvular disease and can be a devastating illness. An effective prophylactic course is needed for persons who undergo diagnostic and therapeutic procedures, and studies of the most effective measures should be undertaken.

Monitoring and secondary prevention depend on adequate laboratory tests. A national reference laboratory should be supported to preserve and to maintain valuable collections of reference strains and antisera and to ensure the continued availability of reliable, internationally comparable typing sera for qualified investigation in the United States. The search must continue for more specific antibodies and for more rapid and reliable diagnosis of streptococcal presence in the pharynx, which predicts increased risk of rheumatic fever and rheumatic heart disease.

Recommendations

1. To discover the causes of and best therapy for congenital heart disease, a unified form of data collection is needed. To accomplish this goal, the NIH (NHLBI) should organize a workshop to discuss the method of establishing a unified reporting system for congenital heart disease along with other birth defects and other cardiac disorders such as cardiomyopathy. This is particularly important in studying the recent apparent increase in patent ductus arteriosus and ventricular septal defect and the possible causes for this increase. The feasibility of such a system should be evaluated in terms of cost and benefit. The capability of existing data collection systems at the CDC, CC or NCHS and their expansion should be considered.

2. Patent ductus arteriosus is a frequent cause of morbidity and mortality in the premature infant. A prospective study of the incidence, management, and etiology of patent ductus ateriosus in preterm infants should be undertaken under the auspices of NHLBI. From this, a clearer picture of the magnitude of the problem facing health care delivery systems can be defined. In addition, clinical trials of the use of prostaglandin inhibitors that cause closure of the ductus arteriosus should be undertaken with a long-term study of different management schemes. The long-term effects of indomethacin must be studied before general acceptance of this form of therapy can be recommended for all newborn infants with patent ductus arteriosus.

3. Rheumatic fever and heart disease have not been eliminated. Therefore, NHLBI, in collaboration with the Center for Disease Control, Crippled Children's Program, state health departments, and local volunteer organizations, should encourage the study of various existing prevention strategies for rheumatic fever and rheumatic heart disease to determine the most effective way to eradicate these diseases. NHLBI should sponsor a workshop or series of workshops to consider what kinds of studies should be done to learn how long and what kinds of primary and secondary prevention should be practiced.

Research into Epidemiologic and Biometric Methods

In biological studies of population groups, an attempt is made to identify or unmask those host and environmental factors and conditions that cause disease or can lead to its control. Epidemiologic and biometric techniques need to be sharpened if greater understanding of cardiovascular diseases is to be achieved--and from this understanding, control of these diseases.

This section of the task force report identifies some special problems in epidemiologic and biometric methods. These are dealt with under five main headings: I. Measures of Exposure to Causes of Disease; II. Measures of Clinical and Subclinical Disease; III. Collaboration among Disciplines and Organizations; IV. Special Opportunities and Problems; and V. Handicaps and Limitations. Other recommendations for the development of specific methodologies are dealt with in other sections of this task force report.

I. Measures of Exposure to Causes of Disease

Knowledge is still limited on how to measure, easily and cheaply, what people are exposed to that may affect people's health. Since exposure may be continuous, sporadic, or intermittent, techniques to assess these aspects are needed. For example, new instruments for continuous monitoring of blood pressure are needed, as are new statistical techniques to use these data most efficiently. This is just one example of the need for better methods to assess changes in biological characteristics as measures of risk.

A. Identification and Classification of Host Characteristics

1. Physical Activity

It is strongly argued that regular, vigorous physical exercise promotes physical and mental well-being, reduces the frequency and level of characteristics related to CHD, leads to cardiorespiratory fitness, and prevents CHD. Additional research is needed to assess the validity of these inferences and to identify the kind, frequency, duration, and intensity of physical exercise that would produce these salutary effects.

Exercise comes chiefly from leisure activities, since modern sedentary occupations rarely demand sufficient energy output to produce a beneficial effect. An evaluation of patterns of physical activity calls for research into total energy output (possibly by questionnaire, as well as by direct recording) and its continuous monitoring to distinguish regular levels from bursts of output and to determine if different patterns of output have different health effects. Studies are needed on the effects of age, sex, etc. Methods of identifying not only optimal but detrimental levels of physical exercise need to be developed, including measuring the effects of age- and time-related changes in exercise patterns.

2. Other Host Behavior

There is evidence that faulty diet increases the risk of CHD and other hypertensive-arteriosclerotic diseases. Further knowledge is needed as to

the detailed constituents making up a faulty diet. Improved methods are needed to measure the quality and quantity of lifetime habits of food consumption and their interaction with other personal CVD risk factors (physical, psychosocial, and cultural). The development and evaluation of objective blood chemical measurements to determine dietary intake of individuals, especially types of fat and cholesterol, should be given emphasis. Along with improved methods of gauging dietary practices, methods to quantify metabolic processes of large numbers of people, personality typologies (A and B), and their interrelationships need development.

Work should be further encouraged on the development and assessment of better methods for ascertaining personal habits such as smoking, drinking, salt consumption, and drug-taking. These habits change over time, and the composition of cigarettes, drinks, foods, and drugs likewise changes, thus requiring continuous monitoring, or at least frequent periodic monitoring.

3. Risk Factors Related to Internal Environment

Higher levels of blood pressure and abnormal blood lipid patterns are among the strongest predictors of later cardiovascular disease. Improved measurements of the levels of these risk factors and their changes over time are needed. Continuous blood pressure recordings could lead to improved understanding of the relationship between systolic and/or diastolic hypertension and specific CV diseases. Better micromethods to quantify plasma lipids and lipoproteins, especially for pediatric use, and improved immunochemical techniques to permit testing of hormone levels on large numbers of persons are needed.

B. Risk Factors of the External Environment

Dietary practices alter CVD risks, although it is not known when in life and for how long one has to be exposed to increase the risk of CVD. The effects of several food constituents (e.g., fiber, sugar, animal vs. vegetable proteins, salt, alcohol) and contaminants (stabilizers, fortifiers, emulsifiers, coloring materials, preservatives, etc.) on the induction of pathologic changes in the CV system remain to be elucidated in detail. Improved methods are needed for identifying and quantifying intakes of such substances that would have application in large populations--for assessment of both individuals and groups.

Monitoring of individuals and groups for exposures to man's exogenous environment--for example, to air and water pollutants, trace elements (such as heavy elements) in food, water and in the air, and potentially hazardous workplace chemicals--should give data leading to further testing of presumptive causes of CVD. Further work is needed on the optimal criteria for identification of adequate comparison groups in studies of occupational or environmental exposures as they relate to cardiovascular disease occurrence.

A personal-number identification system is needed that permits nonintrusive, nonprivacy-invading followup.

C. Familial Factors

Familial factors range from inherited characteristics, to way of life,

to shared environmental exposures. All these may be related to susceptibility or resistance to disease. Methods for studying familial resemblance in risk factors and for defining variance in physical and physiological attributes need further development, including methods for assessing the contributions to heart disease of genes, shared environment, environments specific to individual members of the family, and their interaction. The changing composition of families creates problems and opportunities in studying individuals who are related to one another by blood in varying degrees (or not at all) and who live together in the same household for varying periods of time.

Recent developments in population genetics have direct application to the investigation of the origins and progression of risk factors for heart disease. However, communication and transmittal of information about these new methods among geneticists, epidemiologists, and clinicians have been slow. Collaboration among such biomedical scientists should be fostered through periodic workshops, structured around new methodologic developments of promise.

D. Validation and Standardization of Measurements

The possibility of success of epidemiologic studies is increased when workers use standardized observations and make precise classifications of persons according to the presence, absence, or specific levels of host-environmental characteristics and the disease under study. The reliability of biological measurements may be affected either by variability in the measurement process itself or by individual biological variability. Many present methods of measuring validity and reliability need refinement. If comparisons are to be made among different studies, uniform methods must be used. For example, the National Lipoprotein Standardization Program has led to the use of uniform procedures and has permitted pooling and comparison; similar standardization is desirable for blood pressure, exercise, dietary, and biochemical measures. Nonstandard methods often lead to apparent contradictory findings--leading in turn to lost time and effort in trying to resolve the "contradictions."

II. Measures of Clinical and Subclinical Disease

Concepts of disease change when methods of diagnosis change. Epidemiological studies are enriched by progress in refining and standardizing methods of diagnosis. Thus, investigations of hypertensive and arteriosclerotic disease are in need of improved methods (particularly, noninvasive methods applicable in the general population) and agreed-upon objective criteria for their early identification. Hypertension is without symptoms until its late stages; the evaluation of blood pressure is handicapped by sizable intraindividual variability. Arteriosclerotic changes, with early beginnings in childhood, often reveal themselves as catastrophic attacks in middle life or later. Methods of detecting and quantifying presymptomatic disease are necessary for both investigative and control purposes, since often only preclinical disease is treatable and reversible.

A. Preclinical and Premonitory Events

Arteriography and other modern invasive techniques for detecting vascular narrowing, adequacy of heart valve functioning, and myocardial damage cannot be used in large-scale population studies. Noninvasive techniques to detect atherosclerotic lesions and narrowing of coronary, cerebral, and peripheral arteries could identify precursors of CVD and their early pathologic changes. If the extent of atherosclerotic lesions could be quantified by noninvasive techniques, then epidemiologic research could fruitfully use the whole new set of endpoints, and effectiveness of intervention measures could be much more easily assessed.

The costs of most sophisticated equipment are high. Pooling of such equipment for use in multiple study centers is necessary. Methods of measuring and interpreting long-term recording of ECG patterns, blood pressure levels, pulse rates, blood chemistry levels, etc., are also important in working for a new level of understanding of specific events or changes that are followed by later clinical disease.

B. Clinical Events

Methods of providing systematic and possibly frequent sampling of representative sections of large populations are needed to measure the incidence and prevalence of specific nonfatal CVD. Such sampling will give information on trends in disease occurrence by geographic, sociocultural-ethnic, and personal characteristics and will enhance knowledge of risk factors (known, suspected, and unknown). Further work is needed on how to handle data on competing causes of death that remove susceptibles from the population.

Existing data banks (NCHS and others) of large population samples should provide opportunities for long-term followup.

There needs to be exploitation of existing (and often dormant) data sets of community and other population groups on whom initial host-environmental characterization was accomplished years ago. Examples include the Tecumseh, Mich., Population Laboratory, where observations began in the 1950's, and the Oakland, Calif., Child Development Study, which began with the children born in 1960 of women enrolled in a prepaid health plan.

C. Validation and Standardization of Measurements

The identification of specific clinical and subclinical diseases calls for agreement and precision in classification, i.e., improved means of validating diagnoses and demonstrating the reliability of their detection.

III. Collaboration Among Disciplines and Organizations

Epidemiology requires the application of clinical judgment, substantial knowledge of the disease, inductive reasoning, statistical methodology, scholarship. Current attention to epidemics of CVD and other chronic ailments requires more collaboration with clinicians to help devise improved methods of disease assessment and to assist with the evaluation of clinical procedures in chronic disease areas.

The epidemiologist must deal not only with clinical and sociological observations, but also with data from genetics, biochemistry, endocrinology, statistics, et al. Optimal progress through epidemiologic studies will depend on interactions among scientists with a wide range of skills, and on cooperation and collaboration among different organizations, public and private.

A. Mathematical and Statistical Biology

Research in CVD must include increased emphasis on statistical modeling of "host-agent-disease" relationships, i.e., theoretical exploration of the sequence of events involving susceptible individuals, potential disease-causing elements, pathogenetic mechanisms, and subclinical disease and the eventuation of clinical events. Such theoretical work in mathematical epidemiology has aided in our understanding of the causes, pathogenesis, and mechanisms of the spread of specific infectious diseases, and possibly cancer.

In generating etiologically oriented hypotheses, new techniques are needed for searching the large data banks compiled from epidemiologic studies and routinely collected information from Federal agencies (National Center for Health Statistics, Bureau of the Census, etc.) are needed.

New biometric techniques are needed to facilitate elucidation of interrelationships among risk factors, their interactions, nonlinear responses, prediction of the effect of differing "latent periods" and threshold phenomena (for example, the consequences of starting or stopping smoking, of altering diet, and of changing exercise habits), and the measurement of change in causes and effects--trend detection by time, place, and personal characteristics.

Improved techniques are needed for the analysis of time series data and multiple measurements, for handling the effects of major discontinuities in exposures or behavior or the effects of short-term exposure to possible risk elements.

Improved analysis techniques are needed for measuring the effects of intervention, inluding compliance and adherence. For multiple intervention trials, improved statistical techniques are needed to enhance the ability to determine the effects of individual interventions.

Families provide a good research unit, but better measures are also needed of the extent of social interactions among relatives to enhance the ability to sort out which effects are more dependent on inherent genetic factors, as opposed to those arising more from a common environment. Better techniques are needed for evaluating possible interaction of genetic predisposition and environment.

B. Clinical Trials

Planned intervention is now being applied in population groups, for example, to induce individuals or communities to change lifestyles (stop smoking, lose weight, alter diet, increase physical activity--singly or in

combination) and measure incidence of subsequent CVD. A trial--as distinct from a demonstration, pilot, or mass public health project--generally must include adequate comparison populations on whom no intervention techniques are applied, in addition to before-and-after measurements in the test population.

Many aspects of traditional medical care lack a scientific basis. Clinical trials can assess only a small proportion of new treatments. Other methods must be devised to evaluate the efficacy of both established and new treatments and to assess such aspects of medical care as place, duration, type of treatment, and compliance of the patient with medical advice. New approaches to modifying health behavior pose new problems; research is needed into better methods for modifying behavior and for evaluating the outcome of the intervention. Similarly, the translation of new knowledge from the laboratory to the bedside or the community requires research into methods for achieving this and for evaluating the effect of the activity.

Beyond support of additional intervention studies, attention should be given to collaborative arrangements among centers to increase sample sizes through data pooling. Special problems to be faced include the relevance and confidence that can be attached to early stopping systems; using subclinical, preclinical, premonitory disease, and risk factors as endpoints meaningfully related to clinical disease; selection of control populations for appropriate comparisons (as mentioned above); and inclusive of other intervention techniques than those presumed to influence CVD to measure any effect on the incidence of other diseases.

IV. Special Opportunities and Problems

A. Surveillance Techniques

Broadly based monitoring systems are needed for ongoing surveillance of environmental characteristics (and their change) as they relate to CVD occurrence. Population sampling procedures--for example, decisions on the use of representative community groups as well as special geographic-socioeconomic ethnic segments or genetic isolates--deserve further study. The monitoring of lifestyle trends--for example, changes in established risk factors among specific age classes (children, youth, adults) and birth-cohorts--needs special emphasis. Where adequate sample sizes can be developed, study of twins reared apart should be encouraged. Twin registers (for example, NAS/NRC veteran's followup agency registry) should be exploited.

B. Long-term Followup

For thorough-going evaluation of the natural history of relationships between specific risk factors and cardiovascular diseases, long-term and repeated monitoring of specific populations will be required. Improved monitoring methods to establish and maintain such continuing followup and evaluation should be developed.

C. Identification and Exploitation of Existing Data Banks

There should be continued observations on the Framingham population, both the original and second-generation cohorts. Also, other NHLBI epidemiologic projects in Hawaii and Puerto Rico should be supported fully (as in Framingham), including adequate commitment for long-term funding and with coordination of interests among other public and private health agencies, including other disease-oriented groups such as NCI and the National Institute on Aging. Similar population-based studies--for example, those in Albany, New York, the several in Chicago, in Tecumseh, Mich., in Evans County, Ga., and that in Los Angeles--require similar long-term exploitation.

Other data banks that should be exploited for their epidemiologic and biostatistical worth include U.S. health survey data (HMO's, HANES, and related systems); industrial and union rosters, member lists of health insurance plans, and lists of employees submitting to preemployment physical examination; Social Security system records; lists of special populations, such as U.S. veterans with government insurance; blood serum banks; and records collected and maintained by other Federal agencies (for example, National Institute of Occupational Safety and Health, Environmental Protection Agency, Department of Defense, etc.). Attention should be directed to foreign data sources, such as Registrar-General records in the United Kingdom on death as related to other vital events, demographic characteristics, and employment; population registers in Norway and Sweden, and twin registers in Denmark and Sweden; and data obtained through the Canadian Health Survey.

V. Handicaps and Limitations

Societal concerns have been appropriately directed toward rights of personal privacy and issues of confidentiality. The rights of study participants must be protected fully by providing adequate safeguards for privacy and confidentiality, consistent with the conducting of epidemiologic and other investigations designed to identify the causes and pathways and the prevention and treatment potential of human disease.

Among the documents that frequently need to be reviewed in the conduct of field studies are employer records, social security records, hospital medical care records (special restrictions have already been applied by the VA), and data originally recorded for other purposes but now useful for medical research purposes (for example, industrial pay, work exposure, and health maintenance records). Much investigation time and attention often must go into obtaining approval from a variety of boards and review committees for such privileges as contacting medical patients, reviewing their records, and obtaining permission to use histological materials and other specimens. Consent forms sometimes are so inclusive that they encourage nonresponse or inappropriately influence response. Legislation to assist the legitimate worker would advance progress.

Recommendations

1. Different scientists taking measurements in a nonstandard way, while believing that they are doing comparable work, can find themselves in apparent conflict. There is need for further standardization of methods used to measure the changing patterns of exposure to potential causes of cardiovascular disease, and the consequences of that exposure.

   NHLBI should encourage, through appropriate support mechanisms, small workshops, the development of improved methods to measure dietary intake, smoking habits, physical activity, alcohol consumption, exposure to environmental pollutants, etc. Better noninvasive methods are needed for making continuous measures of such variables as blood pressure. Some of this should be done in cooperation with agencies that also have a need to monitor the environment--such as the Environmental Protection Agency and NIOSH.

2. It is often difficult to separate the contributions of genetics from the contributions of a common environment shared by persons related to each other. In the United States the basic unit of genetic relationship and shared environment is the family.

   NHLBI should encourage the development of improved techniques for using the family as a unit of sampling for elucidating the nature-nurture interactions.

3. Continuous measurement of activities, exposure, and body functions will lead to enormous masses of data. Present statistical techniques use only a tiny fraction of such time-series type data. New methods need to be developed for the analysis of time-series data and for the allocation of the effects of each of the individual measures of multiple risk factors, and how much modification of these risk factors will change the incidence of coronary heart disease.

   NHLBI should sponsor a workshop on improved methods in mathematical statistics for handling "continuous" data and for estimating the effects of modifying risk factors. Individual investigators should be supported to develop mathematical models of the separate heart diseases, which will provide a better understanding of the relationships among multiple personal and environmental causes and the onset and progress of these diseases.

4. New treatments and new interventions are often introduced without adequate knowledge of their likely effects--or side effects. The common epidemiological methods of evaluating after-the-fact consequences need to be extended to assess the quality of medical practice and the value of interventions.

   NHLBI should sponsor several small, innovative attempts at measuring the quality of medical care and the effects of intervention. The methodological developments should be carried out in cooperation with other agencies (for example, NCI) that are concerned with

measuring the effects of intervention on arresting the development of chronic diseases. Such studies should include further assessment of the effectiveness of surgical intervention (for example, coronary bypass surgery), drug therapy (such as the recently initiated study of the use of prostaglandin inhibitors or indomethacin in the management of patent ductus arteriosus in children), and behavioral techniques used in the prevention or therapy of coronary heart disease. In addition, NHLBI should sponsor a workshop on the preventive strategies for rheumatic fever and rheumatic heart disease. Randomized clinical trials are often difficult and expensive. Alternatives--particularly with respect to measuring the impact of interventions intended to alter behavior patterns in general populations--need to be pursued.

Training Needs in Cardiovascular Epidemiology

Sound epidemiologic research on heart disease requires an adequate number of well-trained epidemiologists. Historically, NHLBI has been a leader in the area of training. Research training programs developed in the 1950's became a model for other Federal agencies. More recently, the reactivation of predoctoral and postdoctoral programs in the early 1970's has made a substantial contribution. The 10-day course in cardiovascular epidemiology jointly sponsored by NHLBI and the American Heart Association has, for the past 4 years, provided a bridge between the specialties of cardiology and epidemiology.

Today, however, not enough medical doctors are becoming epidemiologists. Private practice and clinical specialties usually pay much more. Something has to be done to get more physicians into epidemiology.

Major efforts should be directed to recruiting physicians early in their professional careers, before income levels become so high that transition becomes economically difficult. The critical period is during and immediately following the clinical residency. Young resident physicians are often able to "moonlight," thereby supplementing their residency stipends. Such opportunities are usually not available to epidemiology trainees.

NHLBI should be encouraged to develop educational programs in cooperation with epidemiology departments in schools of public health and with departments of preventive medicine that have faculty strength in cardiovascular epidemiology. An increased flow of physicians into existing training facilities should be the initial goal. Stipend levels adequate to compete for the best young medical talent should be developed, and these levels should permit compensation to offset the lack of moonlighting opportunities.

In addition to didactic training leading to the master of public health degree with specialization in epidemiology or its equivalent, existing residency programs in preventive medicine should receive support in the form of adequate stipend levels. Institutional training grants to provide cost-sharing incentives should be expanded to help offset the costs to hard-pressed academic institutions.

Another training resource that should be developed is the existing epidemiology research programs at NHLBI (and other Institutes of NIH), CDC, and NCHS. Selective recruitment of physicians who do not wish to choose university-based training programs may provide an alternate avenue to developing epidemiologists. An existing model for this approach is the Epidemic Intelligence Service, sponsored by CDC, which has provided excellent training for young epidemiologists interested in infectious diseases. Similar programs might be developed for chronic disease research.

Good epidemiologic research requires good investigators trained in good centers. Innovation and increased flexibility of federally assisted training programs will be required if the most able young physicians are to be attracted to this field.

Recommendations

1. NHLBI should expand educational programs in cooperation with epidemiological departments in schools of public health and departments of preventive medicine in schools of medicine that have substantial strength in cardiovascular epidemiology. At least 8 to 10 of these programs should be started, and they should have the following characteristics:

   - Training of both epidemiolgists and biostatisticians, as many as, but not more than, 4 positions for each of the 2 fields in each of 3 years in the program, i.e., a maximum of 24 trainees in any one program.

   - Stipends that are competitive with other training opportunities sufficient to attract young M.D.'s as well as other predoctoral and postdoctoral candidates.

   - Institutional support to the departments conducting the training programs, to the extent of one faculty member, one research assistant, and one-half secretary as well as modest funds for research operations for each six trainees.

   - Arrangements for on-the-job training with Federal, state, and local agencies.

   - Support extending over a 5-year period.

Glossary

Angina Pectoris: An episode of chest pain due to a temporary discrepancy between the supply and demand of oxygen to the heart. This may be due to low oxygen levels in the blood (from smoking or respiratory disease), to a restricted bloodflow to the heart (coronary insufficiency), or to an increase in heart work beyond normal levels. Most often, angina pectoris is a chronic condition caused by a blood supply restricted by hardening and narrowing of the coronary arteries supplying the heart muscle (coronary atherosclerosis).

An angina attack is not to be confused with a heart attack (myocardial infarction), which results from a severe and prolonged lack of oxygenated blood to a part of the heart.

Arteriosclerosis: A group of diseases characterized by thickening and loss of elasticity of artery walls. This may be due to an accumulation of fibrous tissue, fatty substances (lipids), and/or minerals. (See Atherosclerosis.)

Aspirin Myocardial Infarction Study (AMIS): An NHLBI study involving 30 clinical centers to determine whether administration of aspirin to persons who have had at least one documented heart attack will result in a significant reduction in cardiovascular morbidity and mortality.

Atherosclerosis: A kind of arteriosclerosis in which the inner layer of the artery wall is made thick and irregular by deposits of a fatty substance. These deposits (called atheromata or plaques) project above the surface of the inner layer of the artery, and thus decrease the diameter of the internal channel of the vessel. (See Arteriosclerosis.)

Behavior, Type A and Type B: Two kinds of behavior patterns, as recognized in medicine. Type A behavior is characterized by high degrees of competitiveness, aggressiveness, and feelings of the pressure of time. This type of behavior is thought by some cardiologists to be a risk factor in the development of coronary heart disease. Individuals with the converse Type B behavior are more easygoing and contemplative and more easily satisfied.

Cardiomyopathy: A general diagnostic term for diseases that involve mainly the myocardium (heart muscle) and not other heart structures (such as the valves, coronary vessels, or pericardium). They may be caused by known toxic or infectious agents. For the majority of cases, however, the cause is not known.

Cardiovascular Disease: Diseases of the heart such as rheumatic heart disease, coronary heart disease, and myocardial insufficiency, as well as stroke, hypertension, and generalized arteriosclerosis.

Cardiovascular-Renal Disease: Disease involving the heart, blood vessels, and kidneys.

Cholesterol: A fatlike substance found in animal tissue. In blood tests, the normal level for Americans is assumed to be between 180 and 230 mg per 100 cc. A higher level is often associated with high risk of coronary atherosclerosis.

Coronary Artery Surgery Trial (CAST): An NHLBI trial involving 16 clinical centers to evaluate the efficacy of coronary artery bypass surgery and its potential therapeutic effect in reducing morbidity and mortality in coronary artery disease.

Coronary Atherosclerosis: Commonly called coronary heart disease. An irregular thickening of the inner layer of the walls of the arteries which conduct blood to the heart muscle. The internal channel of these arteries (the coronaries) becomes narrowed, and the blood supply to the heart muscle is reduced. (See Atherosclerosis.)

Coronary Heart Disease: Also called coronary artery disease and ischemic heart disease. Heart ailments caused by narrowing of the coronary arteries and therefore a decreased blood supply to the heart (ischemia).

Epidemiology: The science dealing with the factors which determine the frequency and distribution of a disease in a human community.

Framingham Study: A 28-year NHLBI study to examine the natural history of atherosclerosis and hypertension and factors that predispose persons to heart attack. Every 2 years, 5,200 men and women (30 to 60 years old in 1950) and their offspring have been examined for the presence of coronary heart disease, cerebral vascular disease, and associated risk factors.

Heart Attack: The death of a portion of heart muscle which may result in disability or death of the individual, depending on how much of the heart is damaged. A heart attack occurs when an obstruction in one of the coronary arteries prevents an adequate oxygen supply to the heart. Symptoms may be none, mild, or severe and may include chest pain (sometimes radiating to the shoulder, arm, neck, or jaw), nausea, cold sweat, and shortness of breath.

Doctors often refer to a heart attack in terms of the obstruction (i.e., coronary occlusion, coronary thrombosis, or simply "coronary") or of the heart muscle damage (myocardial infarction, "infarct," or "M.I."). In common usage, the term "heart attack" often incorrectly refers to irregular heartbeats or attacks of angina pectoris.

Heart Disease: A general term used to mean ailments of the heart or blood vessels. Some of these are present at birth (congenital) and are either inherited or are the result of environmental influences on the embryo as it develops in the womb. The majority of cases of heart disease, however, are acquired later in life, for example, through the development of atherosclerosis.

High Blood Pressure: An unstable or persistent elevation of blood pressure above the normal range. Uncontrolled, chronic high blood pressure strains the heart, damages the arteries, and creates a greater risk of heart attack, stroke, and kidney problems. Also known as hypertension.

Hypertension: Commonly called high blood pressure.

Hypertension Detection and Followup Program (HDFP): An NHBLI study to determine in the general population the extent to which mortality and morbidity associated with elevated blood pressure can be reduced by systematic antihypertensive drug management. HDFP involves more than 10,940 participants in 14 communities and includes multiple ethnic, racial, and socioeconomic groups.

Lifestyle: An individual's typical way of life, including diet, kinds of recreation, job, home environment, location, temperament, and smoking, drinking, and sleeping habits.

Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT):

A 7-year NHLBI study to test whether lowering cholesterol in hypercholesterolemic but otherwise healthy subjects (Type II hyperlipoproteinemia patients) will reduce or slow the development of premature coronary heart disease. Approximately 3,800 men between the ages of 35 and 59 are participating in 12 LRC centers.

Lipoprotein: A complex consisting of lipid (fat) and protein molecules bound together. Lipids do not dissolve in the blood, but must circulate in the form of lipoproteins.

Morbidity Rate: The ratio of the number of cases of a disease to the number of well people in a given population during a specified period of time, such as a year. The term "morbidity" involves two separate concepts:

1. Incidence is the number of new cases of a disease developing in a given population during a specific period of time, such as a year.
2. Prevalence is the number of cases of a given disease existing in a given population at a specified moment of time.

Mortality Rate, Age-Adjusted: Also called age-adjusted death rate. Death rates which have been standardized for age for the purpose of making comparisons between different populations or within the same population at various intervals of time. The age-specific death rates of the populations being compared are applied to a population that is arbitrarily selected as standard to determine what would be the crude death rate in the standard population if it were exposed first to the rates of one population and then to the rates of the other.

Multiple Risk Factor Intervention Trial (MRFIT): A 6-year NHLBI investigation involving 20 clinical centers and more than 12,000 participants to determine whether a preventive program directed at the reduction of serum cholesterol, reduction of blood pressure, and reduction or elimination of cigarette smoking among a specific group of "high-risk" men will significantly reduce the incidence of myocardial infarction and death from coronary disease.

Pooling Project: A national cooperative project designed to pool the results of five longitudinal investigations on the incidence of coronary heart disease in middle-aged white men. The project included the Albany Civil Servant, Chicago Peoples Gas Co., Chicago Western Electric Co., Framingham Community, and Tecumseh Community Studies.

Rheumatic Heart Disease: The damage done to the heart--particularly, the heart valves--by one or more attacks of rheumatic fever. The valves are sometimes scarred so they do not open and close normally.

Specialized Centers of Research-Atherosclerosis (SCOR-A): A number of grants-supported centers organized to advance basic knowledge and develop most effective methods of clinical management and prevention in the area of atherosclerotic disease. Centers address different but related aspects of atherosclerosis (such as its development in the young) within a coordinated network.

Stroke: Also called cerebrovascular accident. An impeded blood supply to some part of the brain, generally caused by:

1. A blood clot forming in the vessel (cerebral thrombosis).
2. A rupture of the blood vessel wall (cerebral hemorrhage).
3. A blood clot or other material from another part of the vascular system which flows to the brain and obstructs a cerebral vessel (cerebral embolism).
4. Pressure on a blood vessel, as by a tumor.

Thrombosis: The formation or presence of a blood clot (thrombus) inside a blood vessel or cavity of the heart.

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